

CROSS-REFERENCE TO RELATED APPLICATIONS

10 SEQUENCE LISTING

15 BACKGROUND OF THE INVENTION

MAPT transcripts are differentially expressed throughout the body, predominantly in the central and peripheral nervous system. Wild type Tau is involved in stabilizing microtubules in neuronal axons, maintaining dendritic spines, and regulating axonal transport, microtubule dynamics, and cell division. Pathogenic variants of MAPT are found in approximately 10% of patients with primary tauopathy. Variants are primarily missense mutations and localized in exons 9-13 (microtubule binding domains), with many affecting the alternative splicing of exon 10.

There are currently no curative therapies for tauopathies, and treatments are only aimed at alleviating the symptoms and improving the patient's quality of life. Accordingly, there is a need for

agents that can selectively and efficiently inhibit or adjust the expression of the MAPT gene such that subjects having a MAPT-associated disorder, *e.g.*, Alzheimer's disease, FTD, PSP, or another tauopathy, can be effectively treated.

5

BRIEF SUMMARY OF THE INVENTION

The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a MAPT gene. The MAPT gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (MAPT gene) in mammals.

10 The iRNAs of the invention have been designed to target a MAPT gene, *e.g.*, a MAPT gene having a missense and/or deletion mutations in the exons of the gene, and having a combination of nucleotide modifications. The iRNAs of the invention inhibit the expression of the MAPT gene by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control
15 levels, and reduce the level of sense- and antisense-containing foci. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety. In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT,
20 wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO: 4.

25 In another aspect, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2 or
30 SEQ ID NO: 4.

In yet another aspect, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous
35 nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 3-8 and 16-28.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 512-532, 513-533, 514-534, 515-535, 516-536, 517-537, 518-538, 519-539, 520-540, 1063-1083, 1067-1087, 1072-

1092, 1074-1094, 1075-1095, 1125-1145, 1126-1146, 1127-1147, 1129-1149, 1170-1190, 1395-1415, 1905-1925, 1906-1926, 1909-1929, 1911-1931, 1912-1932, 1913-1933, 1914-1934, 1915-1935, 1916-1936, 1919-1939, 1951-1971, 1954-1974, 1958-1978, 2387-2407, 2409-2429, 2410-2430, 2469-2489, 2471-2491, 2472-2492, 2476-2496, 2477-2497, 2478-2498, 2480-2500, 2481-2501, 2482-2502, 2484-
5 2504, 2762-2782, 2764-2784, 2766-2786, 2767-2787, 2768-2788, 2769-2789, 2819-2839, 2821-2841, 2828-2848, 2943-2963, 2944-2964, 2946-2966, 2947-2967, 3252-3272, 3277-3297, 3280-3300, 3281-3301, 3282-3302, 3284-3304, 3285-3305, 3286-3306, 3331-3351, 3332-3352, 3333-3353, 3334-3354, 3335-3355, 3336-3356, 3338-3358, 3340-3360, 3342-3362, 3343-3363, 3344-3364, 3345-3365, 3346-3366, 3347-3367, 3349-3369, 3350-3370, 3353-3373, 3364-3384, 3366-3386, 3367-3387, 3368-3388,
10 3369-3389, 3370-3390, 3412-3432, 3414-3434, 3415-3435, 3416-3436, 3417-3437, 3419-3439, 3420-3440, 3424-3444, 3425-3445, 3426-3446, 3427-3447, 3428-3448, 3429-3449, 3430-3450, 3431-3451, 3434-3454, 4132-4152, 4134-4154, 4179-4199, 4182-4202, 4184-4204, 4395-4415, 4425-4445, 4426-4446, 4429-4449, 4469-4489, 4470-4490, 4471-4491, 4472-4492, 4473-4493, 4474-4494, 4569-4589, 4571-4591, 4572-4592, 4596-4616, 4623-4643, 4721-4741, 4722-4742, 4725-4745, 4726-4746, 4766-
15 4786, 4767-4787, 4768-4788, 4769-4789, 4770-4790, 4779-4799, 4805-4825, 4806-4826, 4807-4827, 4808-4828, 4809-4829, 4812-4832, 4813-4833, 4814-4834, 4936-4956, 5072-5092, 5073-5093, 5345-5365, 5346-5366, 5349-5369, 5350-5370, 5351-5371, 5460-5480, 5461-5481, 5463-5483, 5465-5485, 5467-5487, 5468-5488, 5469-5489, 5470-5490, 5471-5491, 5505-5525, 5506-5526, 5507-5527, 5508-5528, 5509-5529, 5511-5531, 5513-5533, 5514-5534, 5541-5561, 5544-5564, 5546-5566, 5547-5567,
20 5548-5568, 5550-5570, 5551-5571, 5574-5594, 5576-5596, 5614-5634, 521-541, 522-542, 523-543, 524-544, 525-545, 526-546, 527-547, 528-548, 529-549, 530-550, 531-551, 532-552, 533-553, 534-554, 535-555, 536-556, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063, 1044-1064, 1045-1065, 1046-1066, 1047-1067, 1048-1068, 1049-1069, 1050-1070, 1051-1071, 1052-1072, 1053-1073, 1054-1074, 1062-1082, 1064-1084, 1065-
25 1085, 1066-1086, 1068-1088, 1069-1089, 1070-1090, 1071-1091, 1073-1093, 1076-1096, 1077-1097, 1078-1098, 1079-1099, 1080-1100, 1081-1101, 1082-1102, 1128-1148, 1129-1149, 1130-1150, 1131-1151, 1132-1152, 1133-1153, 1134-1154, 1135-1155, 1136-1156, 1137-1157, 1138-1158, 1139-1159, 1140-1160, 1141-1161, 1142-1162, 1143-1163, 1144-1164, 1145-1165, 1146-1166, 1147-1167, 1148-1168, 975-995, 976-996, 977-997, 978-998, 979-999, 980-1000, 981-1001, 982-1002, 983-1003, 984-
30 1004, 985-1005, 986-1006, 987-1007, 988-1008, 989-1009, 990-1010, 991-1011, 992-1012, 993-1013, 994-1014, 995-1015, 996-1016, 997-1017, 998-1018, 999-1019, 1000-1020, 1001-1021, 1002-1022, 1003-1023, 1004-1024, 1005-1025, 1006-1026, 1007-1027, 1008-1028, 1009-1029, 1010-1030, 1011-1031, 1012-1032, 1013-1033, 1014-1034, 1015-1035, 1016-1036, 1017-1037, 1018-1038, 1019-1039, 1020-1040, 1021-1041, 1022-1042, 1023-1043, 1024-1044, 1025-1045, 1026-1046, 1027-1047,
35 1028-1048, 1029-1049, 1030-1050, 1031-1051, 1032-1052, 1033-1053, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063 and 1045-1065 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

In certain embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is complementary over its entire length to a fragment of SEQ ID NO: 4 selected from the group of nucleotides, wherein the sense strand comprises at least 15 contiguous nucleotides
5 differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 520-541, 520-556, 510-534, 512-536, 516-541, 516-540, 520-544, 524-547, 526-551, 529-556, 532-556, 1065-1089, 1068-1095, 1068-1094, 1075-1100, 1076-1100, 1079-1103, 1123-1147, 1127-1151, 1130-1155, 1903-1934, 1903-1930, 1914-1940, 1949-1975, 2470-2497, 2941-2965, 3275-3302, 3278-3302, 3329-3353, 3333-3357, 3338-3367, 3338-3366, 3348-3390, 3348-3388, 3351-3385, 5507-5562
10 and 5549-5597 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 977-997, 980-1000, 973-993, 988-1008, 987-1007, 972-992, 979-999, 1001-1021, 976-996, 994-1014, 1002-1022,
15 978-998, 974-994, 520-540, 521-541, 5464-5484, 1813-1833, 2378-2398, 3242-3262, 5442-5462, 1665-1685, 524-544, 5207-5227, 4670-4690, 3420-3440, 3328-3348, 5409-5429, 5439-5459, 4527-4547, 5441-5461, 5410-5430 and 5446-5466 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides
20 differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-523561.1,
25 AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1, AD-526993.1, AD-1397070.1, AD-1397070.2, AD-1397071.1, AD-1397071.2, AD-1397072.1, AD-1397072.2, AD-1397073.1, AD-1397073.2, AD-1397074.1, AD-1397074.2, AD-1397075.1, AD-1397075.2, AD-1397076.1, AD-1397076.2, AD-1397077.1, AD-1397077.2, AD-1397078.1, AD-1397078.2, AD-
30 1397250.1, AD-1397251.1, AD-1397252.1, AD-1397253.1, AD-1397254.1, AD-1397255.1, AD-1397256.1, AD-1397257.1, AD-1397258.1, AD-1397259.1, AD-1397260.1, AD-1397261.1, AD-1397262.1, AD-1397263.1, AD-1397264.1, AD-1397265.1, AD-1423242.1, AD-1423243.1, AD-1423244.1, AD-1423245.1, AD-1423246.1, AD-1423247.1, AD-1423248.1, AD-1423249.1, AD-1423250.1, AD-1423251.1, AD-1423252.1, AD-1423253.1, AD-1423254.1, AD-1423255.1, AD-
35 1423256.1, AD-1423257.1, AD-1423258.1, AD-1423259.1, AD-1423260.1, AD-1423261.1, AD-1423262.1, AD-1423263.1, AD-1423264.1, AD-1423265.1, AD-1423266.1, AD-1423267.1, AD-1423268.1, AD-1423269.1, AD-1423270.1, AD-1423271.1, AD-1423272.1, AD-1423273.1, AD-1423274.1, AD-1423275.1, AD-1423276.1, AD-1423277.1, AD-1423278.1, AD-1423279.1, AD-1423280.1, AD-1423281.1, AD-1423282.1, AD-1423283.1, AD-1423284.1, AD-1423285.1, AD-

1423286.1, AD-1423287.1, AD-1423288.1, AD-1423289.1, AD-1423290.1, AD-1423291.1, AD-1423292.1, AD-1423293.1, AD-1423294.1, AD-1423295.1, AD-1423296.1, AD-1423297.1, AD-1423298.1, AD-1423299.1, AD-1423300.1, AD-1397266.1, AD-1397266.2, AD-1397267.1, AD-1423301.1, AD-1397268.1, AD-1397268.2, AD-1397269.1, AD-1423302.1, AD-1397270.1, AD-5 1397270.2, AD-1397271.1, AD-1397271.2, AD-1397272.1, AD-1423303.1, AD-1397273.1, AD-1423304.1, AD-1397274.1, AD-1423305.1, AD-1397275.1, AD-1423306.1, AD-1397276.1, AD-1397277.1, AD-1397277.2, AD-1397278.1, AD-1397279.1, AD-1397280.1, AD-1397281.1, AD-1397282.1, AD-1397283.1, AD-1397284.1, AD-1397285.1, AD-1397286.1, AD-1397287.1, AD-1397079.1, AD-1397079.2, AD-1397288.1, AD-1397289.1, AD-1397290.1, AD-1397080.1, AD-10 1397080.2, AD-1397291.1, AD-1397292.1, AD-1397293.1, AD-1397294.1, AD-1397081.1, AD-1397081.2, AD-1397295.1, AD-1397082.1, AD-1397082.2, AD-1397083.1, AD-1397083.2, AD-1397296.1, AD-1397297.1, AD-1397298.1, AD-1397299.1, AD-1397300.1, AD-1397301.1, AD-1397302.1, AD-1397084.1, AD-1397085.1, AD-1397086.1, AD-1397303.1, AD-1397087.1, AD-1397087.2, AD-1397304.1, AD-1397305.1, AD-1397306.1, AD-1397307.1, AD-1397308.1, AD-15 1397309.1, AD-1397310.1, AD-1397311.1, AD-1397312.1, AD-1397313.1, AD-1397314.1, AD-1397315.1, AD-1397316.1, AD-1397317.1, AD-1397318.1, AD-1397319.1, AD-1397320.1, AD-1397321.1, AD-1397322.1, AD-1397088.1, AD-1397089.1, AD-1397090.1, AD-1397091.1, AD-1397092.1, AD-1397093.1, AD-1397094.1, AD-1397095.1, AD-1397096.1, AD-1397097.1, AD-1397098.1, AD-1397099.1, AD-1397101.1, AD-1397102.1, AD-1397103.1, AD-1397104.1, AD-20 1397105.1, AD-1397106.1, AD-1397107.1, AD-1397108.1, AD-1397109.1, AD-1397110.1, AD-1397111.1, AD-1397112.1, AD-1397113.1, AD-1397114.1, AD-1397115.1, AD-1397116.1, AD-1397117.1, AD-1397118.1, AD-1397119.1, AD-1397120.1, AD-1397121.1, AD-1397122.1, AD-1397123.1, AD-1397124.1, AD-1397125.1, AD-1397126.1, AD-1397127.1, AD-1397128.1, AD-1397129.1, AD-1397130.1, AD-1397131.1, AD-1397132.1, AD-1397133.1, AD-1397134.1, AD-25 1397135.1, AD-1397136.1, AD-1397137.1, AD-1397138.1, AD-1397139.1, AD-1397140.1, AD-1397141.1, AD-1397142.1, AD-1397143.1, AD-1397144.1, AD-1397145.1, AD-1397146.1, AD-1397147.1, AD-1397148.1, AD-1397149.1, AD-1397150.1, AD-1397151.1, AD-1397152.1, AD-1397153.1, AD-1397154.1, AD-1397155.1, AD-1397156.1, AD-1397157.1, AD-1397158.1, AD-1397159.1, AD-1397160.1, AD-1397161.1, AD-1397162.1, AD-1397163.1, AD-1397164.1, AD-30 1397165.1, AD-1397166.1, AD-1397167.1, AD-1397168.1, AD-1397169.1, AD-1397170.1, AD-1397171.1, AD-1397172.1, AD-1397173.1, AD-1397174.1, AD-1397175.1, AD-1397176.1, AD-1397177.1, AD-1397178.1, AD-1397179.1, AD-1397180.1, AD-1397181.1, AD-1397182.1, AD-1397183.1, AD-1397184.1, AD-1397185.1, AD-1397186.1, AD-1397187.1, AD-1397188.1, AD-1397189.1, AD-1397190.1, AD-1397191.1, AD-1397192.1, AD-1397193.1, AD-1397194.1, AD-35 1397195.1, AD-1397196.1, AD-1397197.1, AD-1397198.1, AD-1397199.1, AD-1397200.1, AD-1397201.1, AD-1397202.1, AD-1397203.1, AD-1397204.1, AD-1397205.1, AD-1397206.1, AD-1397207.1, AD-1397208.1, AD-1397209.1, AD-1397210.1, AD-1397211.1, AD-1397212.1, AD-1397213.1, AD-1397214.1, AD-1397215.1, AD-1397216.1, AD-1397217.1, AD-1397218.1, AD-1397219.1, AD-1397220.1, AD-1397221.1, AD-1397222.1, AD-1397223.1, AD-1397224.1, AD-

1397225.1, AD-1397226.1, AD-1397227.1, AD-1397228.1, AD-1397229.1, AD-1397230.1, AD-1397231.1, AD-1397232.1, AD-1397233.1, AD-1397234.1, AD-1397235.1, AD-1397236.1, AD-1397237.1, AD-1397238.1, AD-1397239.1, AD-1397240.1, AD-1397241.1, AD-1397242.1, AD-1397243.1, AD-1397244.1, AD-1397245.1, AD-1397246.1, AD-1397247.1, AD-1397248.1, AD-1397249.1, AD-523565.1, AD-1397072.3, AD-1397073.3, AD-1397076.3, AD-1397077.3, AD-1397078.3, AD-1397252.2, AD-1397257.2, AD-1397258.2, AD-1397259.2, AD-1397263.2, AD-1397264.2, AD-1397309.2, AD-64958.114, AD-393758.4, AD-1397080.3, AD-1397293.2, AD-1397294.2, AD-1397081.3, AD-1397083.3, AD-1397298.2, AD-1397299.2, AD-1397084.2, AD-1397085.2, AD-1397087.3, AD-1397306.2, AD-1397307.2, AD-1397308.2, AD-1397088.2, AD-1566238, AD-1566239, AD-1566240, AD-1566241, AD-1566242, AD-1566243, AD-1566244, AD-1566245, AD-1566246, AD-1091965, AD-1566248, AD-1566249, AD-1566250, AD-1091966, AD-1566251, AD-1566252, AD-1566253, AD-1566254, AD-1566255, AD-1566256, AD-1566257, AD-1566258, AD-1566259, AD-692906, AD-1566575, AD-1566576, AD-1566577, AD-1566580, AD-1566581, AD-1566582, AD-1566583, AD-1566584, AD-1566586, AD-1566587, AD-1566588, AD-1566590, AD-1566591, AD-1566634, AD-1566635, AD-1566638, AD-1566639, AD-1566641, AD-1566642, AD-1566643, AD-1566679, AD-1566861, AD-1567153, AD-1567154, AD-1567157, AD-1567159, AD-1567160, AD-1567161, AD-1567164, AD-1567167, AD-1567199, AD-1567202, AD-1567550, AD-1567554, AD-1567784, AD-1567896, AD-1567897, AD-1568105, AD-1568108, AD-1568109, AD-1568139, AD-1568140, AD-1568143, AD-1568144, AD-1568148, AD-1568150, AD-1568151, AD-1568152, AD-1568153, AD-1568154, AD-1568158, AD-1568161, AD-1568172, AD-1568174, AD-1568175, AD-692908, AD-1568176, AD-1569830, AD-1569832, AD-1569834, AD-1569835, AD-1569862, AD-1569872, AD-1569890 and AD-1569892.

In a particular embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1 and AD-526993.1. In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1 and AD-523796.1.

In some embodiments, the nucleotide sequence of the sense and antisense strand comprises any one of the sense and antisense strand nucleotide sequences in any one of Tables 3-8 and 16-28.

In one embodiment, the nucleotide sequence of the sense strand comprises at least 15 contiguous nucleotides corresponding to the MAPT gene exon 10 sense strand sequence set forth in SEQ ID NO: 1533 and an antisense strand comprising a sequence complementary thereto.

5 In one aspect, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 5 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 6.

10 In another aspect, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:6.

15 In yet another aspect, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 12-13.

20 In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 1065-1085, 1195-1215, 1066-1086, 1068-1088, 705-725, 1067-1087, 4520-4540, 3341-3361, 4515-4535, 5284-5304, 5285-5305, 344-364, 5283-5303, 5354-5374, 2459-2479, 1061-1081, 706-726, 972-992, 4564-4584, 995-1015, 4546-4566, 968-988, 1127-1147, 4534-4554, 158-178, 4494-4514, 1691-1711, 3544-3564, 198-218, 979-999, 4548-4568, 4551-4571, 543-563, 715-735, 542-562, 352-372, 362-382, 4556-4576, 4547-4567, 4542-4562, 4558-4578, 4549-4569, 5074-5094, 4552-4572, 5073-5093, 5076-5096, 4550-4570 and 2753-2773 of SEQ ID NO: 5, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 6.

30 In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-393758.1, AD-393888.1, AD-393759.1, AD-393761.1, AD-393495.1, AD-393760.1, AD-396425.1, AD-395441.1, AD-396420.1, AD-397103.1, AD-397104.1, AD-393239.1, AD-397102.1, AD-397167.1, AD-394791.1, AD-393754.1, AD-393496.1, AD-393667.1, AD-396467.1, AD-393690.1, AD-396449.1, AD-393663.1, AD-393820.1, AD-396437.1, AD-393084.1, AD-396401.1, AD-394296.1, AD-395574.1, AD-393124.1, AD-393674.1, AD-396451.1, AD-396454.1, AD-393376.1, AD-393505.1, AD-393375.1, AD-393247.1, AD-393257.1, AD-396459.1, AD-396450.1, AD-396445.1, AD-396461.1, AD-396452.1, AD-396913.1, AD-396455.1, AD-396912.1, AD-396915.1, AD-396453.1 and AD-394991.1.

In one embodiment, the sense strand, the antisense strand, or both the sense strand and the antisense strand described herein, is/are conjugated to one or more lipophilic moieties.

In one embodiment, the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

5 In one embodiment, the lipophilic moiety is conjugated via a linker or carrier.

In one embodiment, the lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

In one embodiment, the hydrophobicity of the double-stranded RNA agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNA agent, exceeds 0.2.

10 In one embodiment, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In some embodiments, the dsRNA agent comprises at least one modified nucleotide.

In one embodiment, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand in a dsRNA agent of the present invention are unmodified
15 nucleotides.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand in the dsRNA agent are modified nucleotides.

In some embodiments, at least one of the modified nucleotides of the dsRNA agent is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-
20 O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate,
25 a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofuran-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

In one embodiment, the modified nucleotide of the dsRNA agent is selected from the group
35 consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxythymidine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

In one embodiment, the modified nucleotide of the dsRNA comprises a short sequence of 3'-terminal deoxythymidine nucleotides (dT).

In one embodiment, the modifications on the nucleotides of the dsRNA agent are 2'-O-methyl, GNA and 2'fluoro modifications.

5 In some embodiments, the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage.

In one embodiment, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

In one embodiment, each strand of the dsRNA is no more than 30 nucleotides in length.

10 In one embodiment, at least one strand of the dsRNA agent comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand of the dsRNA agent comprises a 3' overhang of at least 2 nucleotides.

In some embodiments, the double stranded region of the dsRNA agent may be 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length; 23-27
15 nucleotide pairs in length; 19-21 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

In some embodiments, each strand of the dsRNA may have 19-30 nucleotides; 19-23 nucleotides; or 21-23 nucleotides.

In one embodiment, one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand, such as via a linker or carrier.

20 In one embodiment, the internal positions include all positions except the terminal two positions from each end of the at least one strand.

In another embodiment, the internal positions include all positions except the terminal three positions from each end of the at least one strand.

In one embodiment, the internal positions exclude a cleavage site region of the sense strand.

25 In one embodiment, the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

In another embodiment, the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

30 In one embodiment, the internal positions exclude a cleavage site region of the antisense strand.

In one embodiment, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

35 In one embodiment, the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

In one embodiment, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand.

In another embodiment, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

In one embodiment, the internal positions in the double stranded region exclude a cleavage site region of the sense strand.

In one embodiment, the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

In one embodiment, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

In another embodiment, the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

In yet another embodiment, the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

In one embodiment, the lipophilic moiety is conjugated to position 16 of the antisense strand.

In one embodiment, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

In one embodiment, the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl) lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

In one embodiment, the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

In one embodiment, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

In one embodiment, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

In one embodiment, the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

In one embodiment, the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

In one embodiment, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalanyl, pyridazinonyl, tetrahydrofuranyl, and decalanyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

In one embodiment, the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

5 In one embodiment, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

In one embodiment, the lipophilic moiety or targeting ligand is conjugated via a bio-linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

10 In one embodiment, the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

15 In one embodiment, the dsRNA agent further comprises a targeting ligand that targets a neuronal cell.

In one embodiment, the dsRNA agent further comprises a targeting ligand that targets a liver cell.

In one embodiment, the targeting ligand is a GalNAc conjugate.

20 In one embodiment, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

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

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

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

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

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

In one embodiment, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand.

In one embodiment, the phosphate mimic is a 5'-vinyl phosphonate (VP).

In one embodiment, the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

In one embodiment, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

The present invention also provides cells and pharmaceutical compositions comprising a dsRNA agent of the invention and a lipid formulation.

The present invention also provides pharmaceutical compositions for inhibiting expression of a gene encoding MAPT comprising a dsRNA agent of the invention.

The present invention also provides pharmaceutical compositions for selective inhibition of exon 10-containing MAPT transcripts comprising a dsRNA agent of the invention.

In one embodiment, the dsRNA agent is in an unbuffered solution, such as saline or water.

In another embodiment, the dsRNA agent is in a buffer solution, such as a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

In one aspect, the present invention provides a method of inhibiting expression of a MAPT gene in a cell, the method comprising contacting the cell with a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby inhibiting expression of the MAPT gene in the cell.

In another aspect, the present invention provides a method comprises selective inhibition of exon 10-containing MAPT transcripts in a cell, the method comprising contacting the cell with a

dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby selectively degrading exon 10-containing MAPT transcripts in the cell.

In one embodiment, the cell is within a subject.

In one embodiment, the subject is a human.

5 In one embodiment, the subject has a MAPT-associated disorder.

In one embodiment, the subject has a MAPT-associated disorder that is a neurodegenerative disorder.

In one embodiment, the neurodegenerative disorder of the subject is associated with an abnormality of MAPT gene encoded protein Tau.

10 In one embodiment, the abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain.

In one embodiment, the neurodegenerative disorder is a familial disorder.

In one embodiment, the neurodegenerative disorder is a sporadic disorder.

In one embodiment, the MAPT-associated disorder is selected from the group consisting of
15 tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter
20 tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

25 In some embodiments, contacting the cell with the dsRNA agent inhibits the expression of MAPT by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels. In one embodiment, the dsRNA agent inhibits the expression of MAPT by at least about 25%.

30 In some embodiments, inhibiting expression of MAPT decreases Tau protein level in serum of the subject by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels. In one embodiment, the dsRNA agent decreases Tau protein level in serum of the subject by at least about 25%.

35 In one aspect, the present invention provides a method of treating a subject having a disorder that would benefit from reduction in MAPT expression, comprising administering to the subject a therapeutically effective amount of a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby treating the subject having the disorder that would benefit from reduction in MAPT expression.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in MAPT expression, comprising administering to the subject a prophylactically effective amount of a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby preventing at least one symptom in the subject
5 having the disorder that would benefit from reduction in MAPT expression.

In one embodiment, the disorder is a MAPT-associated disorder.

In one embodiment, the disorder is associated with an abnormality of MAPT gene encoded protein Tau.

In one embodiment, the abnormality of MAPT gene encoded protein Tau results in
10 aggregation of Tau in subject's brain.

In one embodiment, the MAPT-associated disorder is selected from the group consisting of tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal
15 dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear
20 palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

In one embodiment, the subject is human.

In one embodiment, the administration of the dsRNA agent of the invention, or the pharmaceutical composition of the invention, causes a decrease in Tau aggregation in the subject's
25 brain.

In one embodiment, the administration of the agent to the subject causes a decrease in Tau accumulation.

In one embodiment, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

30 In another embodiment, the dsRNA agent is administered to the subject intrathecally.

In yet another embodiment, the dsRNA agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture.

In one embodiment, the methods of the invention further comprise determining the level of
35 MAPT in a sample(s) from the subject.

In one embodiment, the level of MAPT in the subject sample(s) is a Tau protein level in a blood, serum, or cerebrospinal fluid sample(s).

In one embodiment, the methods of the invention further comprise administering to the subject an additional therapeutic agent.

In one aspect, the present invention provides a kit comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

5 In another aspect, the present invention provides a vial comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

In yet another aspect, the present invention provides a syringe comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

10 In another aspect, the present invention provides an intrathecal pump comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

BRIEF SUMMARY OF THE FIGURE

FIG.1 shows the AAV screen in liver to determine the effect of RNAi compositions on MAPT expression. Vertical axis indicates human MAPT expression in mice dosed with RNAi compositions relative to the MAPT expression levels in PBS dosed mice.

FIG.2 shows the AAV screen in liver to determine the effect of selected dsRNA agents in Tables 25-26 on the level of both sense- or antisense-containing foci in mice expressing human MAPT RNAs. Vertical axis indicates human MAPT expression in mice dosed with RNAi compositions relative to the MAPT expression levels in PBS dosed mice.

20 FIG.3 shows the AAV screen in liver to determine the effect of selected dsRNA agents in Tables 25-26 on the level of both sense- or antisense-containing foci in mice expressing human MAPT RNAs. Vertical axis indicates human MAPT expression in mice dosed with RNAi compositions relative to the MAPT expression levels in PBS dosed mice.

25 DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a MAPT gene. The MAPT gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (MAPT gene) in mammals.

30 The iRNAs of the invention have been designed to target a MAPT gene, *e.g.*, a MAPT gene either with or without nucleotide modifications. The iRNAs of the invention inhibit the expression of the MAPT gene by at least about 25%, and reduce the level of sense- and antisense-containing foci. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

35 Accordingly, the present disclosure also provides methods of using the RNAi compositions of the disclosure for inhibiting the expression of a MAPT gene or for treating a subject having a disorder

that would benefit from inhibiting or reducing the expression of a MAPT gene, *e.g.*, a MAPT-associated disease, for example, Alzheimer's disease, FTD, PSP, or another tauopathy.

The RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a MAPT gene, *e.g.*, an MAPT exon. In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 21-23 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a MAPT gene.

In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) which can include longer lengths, for example up to 66 nucleotides, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of a MAPT gene. These RNAi agents with the longer length antisense strands preferably include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

The use of these RNAi agents enables the targeted degradation and/or inhibition of mRNAs of a MAPT gene in mammals. Thus, methods and compositions including these RNAi agents are useful for treating a subject who would benefit by a reduction in the levels or activity of a Tau, such as a subject having a MAPT-associated disease, such as Alzheimer's disease, FTD, PSP, or another tauopathy.

The following detailed description discloses how to make and use compositions containing RNAi agents to inhibit the expression of a MAPT gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition or reduction of the expression of the genes.

30 I. Definitions

In order that the present disclosure may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this disclosure.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element, *e.g.*, a plurality of elements.

The term “including” is used herein to mean, and is used interchangeably with, the phrase “including but not limited to.” The term “or” is used herein to mean, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise.

5 The term “about” is used herein to mean within the typical ranges of tolerances in the art. For example, “about” can be understood as about 2 standard deviations from the mean. In certain embodiments, about means $\pm 10\%$. In certain embodiments, about means $\pm 5\%$. When about is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or range.

10 The term “at least” prior to a number or series of numbers is understood to include the number adjacent to the term “at least”, and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, “at least 18 nucleotides of a 21 nucleotide nucleic acid molecule” means that 18, 19, 20, or 21 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that “at least” can modify each of the numbers in the
15 series or range.

As used herein, “no more than” or “less than” is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with an overhang of “no more than 2 nucleotides” has a 2, 1, or 0 nucleotide overhang. When “no more than” is present before a series of numbers or a range, it is understood that “no more than” can
20 modify each of the numbers in the series or range.

As used herein, the term “at least about”, when referring to a measurable value such as a parameter, an amount, and the like, is meant to encompass variations of $\pm 20\%$, preferably $\pm 10\%$, more preferably $\pm 5\%$, and still more preferably $\pm 1\%$ from the specified value, insofar such variations are appropriate to perform in the disclosed invention.
25 For example, the inhibition of expression of the MAPT gene by “at least about 25%” means that the inhibition of expression of the MAPT gene can be measured to be any value $\pm 20\%$ of the specified 25%, i.e., 20%, 30 % or any intermediary value between 20-30%.

As used herein, “control level” refers to the levels of expression of a gene, or expression level of an RNA molecule or expression level of one or more proteins or protein subunits, in a non-
30 modulated cell, tissue or a system identical to the cell, tissue or a system where the RNAi agents, described herein, are expressed. The cell, tissue or a system where the RNAi agents are expressed, have at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 2-fold, 3-fold, 4-fold, 5-fold or more expression of the gene, RNA and/or protein described above from that observed in the absence of the RNAi agent. The % and/or fold difference can be calculated relative to the control
35 levels, for example,

[expression with RNAi agent– expression without RNAi agent]

$$\% \text{ difference} = \frac{\text{expression without RNAi agent}}{\text{expression with RNAi agent}} \times 100$$

As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

In the event of a conflict between a chemical structure and a chemical name, the chemical structure takes precedence.

The term “MAPT” gene, also known as “DDPAC,” “FTDP-17,” “MAPTL,” “MSTD,” “MTBT1,” “MTBT2,” “PPND,” “PPP1R103,” “TAU,” and “microtubule-associated protein tau,” refers to the gene encoding for a protein called microtubule-associated protein tau (MAPT).

The MAPT mRNA is expressed throughout the body, predominantly in the central nervous system (i.e., the brain and the spinal cord) and the peripheral nervous system. Wild type Tau is involved in stabilizing microtubules in neuronal axons, regulating axonal transport and microtubule dynamics, maintaining dendritic spines, and contributing to genomic DNA integrity.

Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Intra- and extra-cellular neuronal Tau aggregates cause microtubule disassembly and axonal degeneration, impaired synaptic vesicle release, and prion-like inter-neuronal spread of tau aggregates called “seeding.”

Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies include, but are not limited to, Alzheimer’s disease, the most common form of presenile dementia that primarily starts with selective memory impairment, and is associated with degeneration of the frontal lobe, temporal lobe (including hippocampus), and parietal lobe of the brain; frontotemporal dementia (FTD), the second most common form of presenile dementia associated with neuronal atrophy of the frontal and temporal lobes, exhibiting a spectrum of behavioral, language, and movement disorders; and progressive supranuclear palsy (PSP), degeneration of brainstem and basal ganglia, exhibiting gaze dysfunction, extrapyramidal symptoms (Parkinsonism symptoms including limb apraxia, akinesia/bradykinesia, rigidity, and dystonia), and cognitive dysfunction, affecting approximately 20,000 people in the United States.

FTD further includes, but are not limited to, behavioral variant frontotemporal dementia (bvFTD), associated pathologically with progressive atrophy in the prefrontal and anterior temporal lobes, and clinically with alterations in complex thinking, personality, and behavior, affecting approximately 30,000 people in the United States; primary progressive aphasia - semantic (PPA-S), degeneration of frontal and temporal lobes associated with difficulty comprehending words and struggle with naming; nonfluent variant primary progressive aphasia (nfvPPA), involving degeneration of left post frontal lobe and insula, and exhibiting poor grammar and inability to understand complex sentences, affecting approximately 1,000 people in the United States; primary progressive aphasia - logopenic (PPA-L), degeneration of the left post/spur temporal lobe and the

medial parietal lobe, associated with difficulty retrieving words and frequent pauses; frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), associated pathologically with degeneration of the frontal and temporal lobes, and clinically with speech and movement impairment; Pick's disease (PiD), degeneration of the frontal and temporal lobes, associated with difficulty in language and thinking and behavioral changes; FTD with motor neuron disease, involving degeneration of the cortex and motor neurons; and corticobasal syndrome (CBS), degeneration of posterior frontal and temporal lobes and basal ganglia [i.e., corticobasal degeneration (CBD)], exhibiting extrapyramidal symptoms (similar to those in Parkinson's disease and PSP) and cognitive dysfunction, affecting approximately 2,000 people in the United States. Mutations of MAPT are reported in approximately 10% of patients with bvFTD, nfvPPA, CBS, and PSP, respectively. MAPT is a major component of neurofibrillary tangles in the neuronal cytoplasm, a hallmark in Alzheimer's disease. The aggregation and deposition of MAPT were also observed in approximately 50% of the brains of patients with Parkinson's disease. Involvement of Tau is indicated in the pathogenesis of other diseases including, but not limited to, argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

The MAPT gene consists of 16 exons (E1-E16). Alternative mRNA splicing of E2, E3, and E10 gives rise to six tau isoforms (352-441 amino acids). E1, E4, E5, E7, E9, E11, E12, E13 are the constitutively spliced exons. E6 and E8 are not transcribed in human brain. E4a is only expressed in the peripheral nervous system. E0 (part of the promotor) and E14 are noncoding exons.

Pathogenic variants in MAPT are found in approximately 10% of patients with primary tauopathy. Variants are primarily missense and localized in exons 9-13 (microtubule binding domains), with many affecting the alternative splicing of exon 10. Examples of coding region mutations include R5H and R5L in E1; K257T, I260V, L266V, G272V, and G273R in E9; N279K, L284L, ΔN296, N296N, N296H, ΔN298, P301L, P301S, P301T, G303V, G304S, S305I, S305N, and S305S in E10; L315R, K317M, S320F, P332S in E11; G335S, G335V, Q336R, V337M, E342V, S352L, S356T, V363I, P364S, G366R, and K369I in E12; G389R, R406W, and T427M in E13 of the MAPT gene. MAPT (tau) null (-/-) humans are likely non-viable. The MAPT heterozygote (+/-) humans have unclear or unknown phenotypes. The MAPT over-expressing (+/++) humans are associated with early onset dementia, FTD, PSP, and CBD.

Each of the six isoforms of the MAPT (tau) protein contains three or four repeated segments (R1, R2, R3, and R4) in its microtubule-binding domain. Each repeat is 31 or 32 amino acids in length. Splicing of E9, E10, E11, and E12 gives rise to the R1, R2, R3, and R4, respectively, of the repeated segments in the MAPT's microtubule-binding domain. Three MAPT (tau) isoforms, in which E10 is spliced in, contain four repeated segments (4R), whereas the other three MAPT isoforms, in which E10 is spliced out, contain three repeated segments (3R).

Translation of E2 and E3 give rise to the N1 and N2 segments, respectively. Alternative splicing of E2 and E3 gives rise to tau isoforms 0N (E2 and E3 are spliced out, resulting in no N segment), 1N (E2 is spliced in and E3 is spliced out, resulting in one N segment), and 2N (E2 and E3 are spliced in, resulting in two N segments). Accordingly, the six MAPT (tau) isoforms resulting from alternative splicing are 2N4R, 1N4R, 0N4R, 2N3R, 1N3R, and 0N3R.

In healthy individuals, the 3R and 4R MAPT transcript isoforms exist in 1:1 ratio. The 3R/4R isoform ratio is skewed in disease states and the ratio predicts the tau aggregate type. The assembly of four-repeat tau into filaments is characteristic of PSP, CBD, argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), and white matter tauopathy with globular glial inclusions (FTD with GGIs), which belong to the FTD spectrum (4R tauopathy). In contrast, in Pick's disease, three-repeat tau predominates in the neuronal inclusions (3R tauopathy). In Alzheimer's disease, or other neurodegenerative diseases with neurofibrillary tangles (NFT dementia), both three- and four-repeat tau isoforms make up the neurofibrillary lesions (3/4R tauopathy). FTLD with MAPT mutations can be 3R, 4R, or 3/4R tauopathy.

FTD with motor neuron disease is associated with the FTLD-TDP43 and FTLD-FUS pathology. It is associated with gene mutations of C9ORF72, FUS, TARDBP, and VCP.

bvFTD is associated with the FTLD-Tau (3R) and FTLD-TDP43 pathology. Ten percent of the cases involve MAPT mutation. It is associated with gene mutations of C9ORF72, GRN, and VCP.

PPA-S may be sporadic. It is associated with the FTLD-TDP43 pathology.

nfvPPA is associated with the FTLD-Tau (4R), Alzheimer's disease, and FTLD-TDP43 pathology, in the order of significance. Ten percent of the cases involve MAPT mutation. nfvPPA is further associated with mutations of GRN.

PPA-L may be sporadic. It is associated with the Alzheimer's disease and FTLD-Tau pathology, in the order of significance.

CBS is associated with the FTLD-Tau (4R) and Alzheimer's disease pathology, in the order of significance. Ten percent of the case is associated with MAPT mutation. The rest of the cases may be sporadic.

PSP involves FTLD-Tau (4R) pathology. Ten percent of the case is associated with MAPT mutation. The rest of the cases may be sporadic.

Tauopathy generally starts at age 60-80 years, and affects the remaining lifespan of 6-10 years. Tauopathies are phenotypically heterogeneous, with variable involvement of motor, cognitive, and behavioral impairment. In particular, progression of motor symptoms is variable.

There are currently no approved disease-modifying therapies for tauopathies. Available treatments are only aimed at alleviating the symptoms and improving the patient's quality of life as the disease progresses. Drugs in preclinical or clinical development include active and passive immunotherapies; inhibitors of O-deglycosylation, aggregation, kinases, acetylation, caspases or tau expression; phosphatase activators; microtubule stabilizers; and modulators of autophagy or proteosomal degradation. Biomarkers and testing used in clinical trials to assess tauopathy include

tau protein phosphorylated at threonine 181 (pTau), total tau protein (tTau), neurofilament light chain (NfL), and volumetric MRI (vMRI).

Exemplary nucleotide and amino acid sequences of MAPT can be found, for example, at GenBank Accession No. NM_016841.4 (Homo sapiens MAPT variant 4, SEQ ID NO: 1, reverse complement, SEQ ID NO: 2); GenBank Accession No. NM_005910 (Homo sapiens MAPT variant 2, SEQ ID NO: 3, reverse complement, SEQ ID NO: 4); GenBank Accession No. NM_001038609.2 (Mus musculus MAPT, SEQ ID NO: 5; reverse complement, SEQ ID NO: 6); GenBank Accession No.: XM_005584540.1 (Macaca fascicularis MAPT variant X13, SEQ ID NO: 7, reverse complement, SEQ ID NO: 8); GenBank Accession No.: XM_008768277.2 (Rattus norvegicus MAPT, variant X7, SEQ ID NO: 9, reverse complement, SEQ ID NO: 10) and GenBank Accession No.: XM_005624183.3 (Canis lupus MAPT variant X23, SEQ ID NO: 11, reverse complement, SEQ ID NO: 12).

The nucleotide sequence of the genomic region of human chromosome harboring the MAPT gene may be found in, for example, the Genome Reference Consortium Human Build 38 (also referred to as Human Genome build 38 or GRCh38) available at GenBank. The nucleotide sequence of the genomic region of human chromosome 17 harboring the MAPT gene may also be found at, for example, GenBank Accession No. NC_000017.11, corresponding to nucleotides 45894382-46028334 of human chromosome 17. The nucleotide sequence of the human MAPT gene may be found in, for example, GenBank Accession No. NG_007398.2

Further examples of MAPT sequences can be found in publically available databases, for example, GenBank, OMIM, and UniProt.

Additional information on MAPT can be found, for example, at the NCBI web site that refers to gene 100128977. The term MAPT as used herein also refers to variations of the MAPT gene including variants provided in the clinical variant database, for example, at the NCBI clinical variants web site that refers to the term mapt.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a MAPT gene, including mRNA that is a product of RNA processing of a primary transcription product (e.g., MAPT mRNA resulting from alternate splicing). In one embodiment, the target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a MAPT gene.

The target sequence is about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in

length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

As used herein, the term “strand comprising a sequence” refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature. “G,” “C,” “A,” “T”, and “U” each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine, and uracil as a base, respectively in the context of a modified or unmodified nucleotide. However, it will be understood that the term “ribonucleotide” or “nucleotide” can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, Table 1). The skilled person is well aware that guanine, cytosine, adenine, thymidine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the disclosure by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the disclosure.

The terms “iRNA”, “RNAi agent,” “iRNA agent,” “RNA interference agent” as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. RNA interference (RNAi) is a process that directs the sequence-specific degradation of mRNA. RNAi modulates, *e.g.*, inhibits, the expression of MAPT in a cell, *e.g.*, a cell within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the disclosure includes a single stranded RNAi that interacts with a target RNA sequence, *e.g.*, a MAPT target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into double-stranded short interfering RNAs (siRNAs) comprising a sense strand and an antisense strand by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes this dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). These siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the disclosure relates to a single stranded RNA (ssRNA) (the antisense strand of a siRNA duplex) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, a MAPT gene. Accordingly, the term “siRNA” is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded RNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded RNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150:883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In another embodiment, a “RNAi agent” for use in the compositions and methods of the disclosure is a double stranded RNA and is referred to herein as a “double stranded RNAi agent,” “double stranded RNA (dsRNA) molecule,” “dsRNA agent,” or “dsRNA”. The term “dsRNA” refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having “sense” and “antisense” orientations with respect to a target RNA, *i.e.*, a MAPT gene. In some embodiments of the disclosure, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, a dsRNA molecule can include ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide, a modified nucleotide. In addition, as used in this specification, an “RNAi agent” may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. As used herein, the term “modified nucleotide” refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or a modified nucleobase. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.*, a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the disclosure include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by “RNAi agent” for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 15-36 base pairs in length, for example, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides or nucleotides not directed to the target site of the dsRNA. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 nucleotides.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. In certain embodiments where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker" (though it is noted that certain other structures defined elsewhere herein can also be referred to as a "linker"). The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs. In one embodiment of the RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

In one embodiment, an RNAi agent of the disclosure is a dsRNA, each strand of which independently comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, a MAPT target mRNA sequence, to direct the cleavage of the target RNA.

In some embodiments, an iRNA of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, *e.g.*, a MAPT target mRNA sequence, to direct the cleavage of the target RNA.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an RNAi agent, *e.g.*, a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively, the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a

nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

5 In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

10 In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

15 In certain embodiments, the overhang on the sense strand or the antisense strand, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes
20 a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are
30 blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double stranded over its entire length.

The term "antisense strand" or "guide strand" refers to the strand of an RNAi agent, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, a
35 MAPT mRNA.

As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, *e.g.*, a MAPT nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the

molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, 3, or 2 nucleotides of the 5'- or 3'-terminus of the RNAi agent. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the antisense strand. In some
5 embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some
10 embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3'-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is
15 not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains
20 no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a MAPT gene,
25 generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a MAPT gene. For example, Jackson *et al.* (*Nat. Biotechnol.* 2003;21: 635–637) described an expression profile study where the expression of a small set of genes with sequence identity to the MAPK14 siRNA only at 12–18 nt of
30 the sense strand, was down-regulated with similar kinetics to MAPK14. Similarly, Lin *et al.*, (*Nucleic Acids Res.* 2005; 33(14): 4527–4535) using qPCR and reporter assays, showed that a 7 nt complementation between a siRNA and a target is sufficient to cause mRNA degradation of the target. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a MAPT gene is important, especially if the particular region of complementarity in a MAPT gene is
35 known to have polymorphic sequence variation within the population.

As used herein, “substantially all of the nucleotides are modified” are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotide.

The term “sense strand” or “passenger strand” as used herein, refers to the strand of an RNAi agent that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

As used herein, the term “cleavage region” refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can be, for example, “stringent conditions”, including but not limited to, 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, *e.g.*, “Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). As used herein, “stringent conditions” or “stringent hybridization conditions” refers to conditions under which an antisense compound will hybridize to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances, and “stringent conditions” under which antisense compounds hybridize to a target sequence are determined by the nature and composition of the antisense compounds and the assays in which they are being investigated. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an RNAi agent, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs. In some embodiments, the “substantially complementary” sequences disclosed herein comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the target MAPT sequence, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. However, where two

oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein.

“Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs or base pairs formed from non-natural and modified nucleotides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms “complementary,” “fully complementary” and “substantially complementary” herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an RNAi agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is “substantially complementary to at least part of” a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding Tau). For example, a polynucleotide is complementary to at least a part of a MAPT mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding Tau.

Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target MAPT sequence. In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of SEQ ID NOs:1, 3, 5, 7, 9 and 11, or a fragment of any one of SEQ ID NOs:1, 3, 5, 7, 9 and 11, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 977-997, 980-1000, 973-993, 988-1008, 987-1007, 972-992, 979-999, 1001-1021, 976-996, 994-1014, 1002-1022, 978-998, 974-994, 981-1001, 995-1015, 1003-1023, 989-1009, 1031-1051, 975-995, 983-1003, 992-1012, 982-1002, 1236-1256, 1023-1043, 986-1006, 1014-1034, 1237-1257, 1030-1050, 997-1017, 1009-1029, 1013-1033, 1027-1047, 998-1018, 1026-1046, 1022-1042, 1065-1085, 1025-1045, 1017-1037, 1006-1026, 1000-1020, 984-1004, 1010-1030, 1064-1084, 1016-1036, 993-1013, 1033-1053, 971-991, 1008-1028, 1032-1052, 1015-1035, 1063-1083, 1020-1040, 985-1005, 999-1019, 1004-1024, 1024-1044, 1104-1124, 990-1010, 1005-1025, 1021-1041, 1028-1048, 996-1016, 1011-1031, 991-1011, 1018-1038, 1228-1248, 1230-1250, 1029-1049, 1019-1039, 1012-1032, 1062-1082, 1231-1251, 1229-1249, 1226-1246, 1227-1247, 975-

997, 978-1000, 971-993, 986-1008, 985-1007, 977-999, 999-1021, 974-996, 992-1014, 1000-1022, 976-998, 972-994, 979-1001, 993-1015, 1001-1023, 987-1009, 1029-1051, 973-995, 981-1003, 990-1012, 980-1002, 1234-1256, 1021-1043, 984-1006, 1012-1034, 1235-1257, 1028-1050, 995-1017, 1007-1029, 1011-1033, 1025-1047, 996-1018, 1024-1046, 1020-1042, 1063-1085, 1023-1045, 1015-1037, 1004-1026, 998-1020, 982-1004, 1008-1030, 1062-1084, 1014-1036, 991-1013, 1031-1053, , 1006-1028, 1030-1052, 1013-1035, 1018-1040, 983-1005, 997-1019, 1002-1024, 1022-1044, 988-1010, 1003-1025, 1019-1041, 1026-1048, 994-1016, 1009-1031, 989-1011, 1016-1038, 1226-1248, 1228-1250, 1027-1049, 1017-1039, 1010-1032, 1229-1251, 1227-1249, 1224-1246, and 1225-1247 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 520-540, 521-541, 5464-5484, 1813-1833, 2378-2398, 3242-3262, 5442-5462, 1665-1685, 1816-1836, 4667-4687, 3183-3203, 3422-3442, 3326-3346, 2379-2399, 3338-3358, 5446-5466, 5440-5460, 5410-5430, 3246-3266, 3181-3201, 2297-2317, 2380-2400, 3328-3348, 5460-5480, 3184-3204, 3420-3440, 3321-3341, 4529-4549, 5473-5493, 5466-5486, 5439-5459, 5369-5389, 4528-4548, 3338-3358, 4670-4690, 3421-3441, 2298-2318, 5444-5464, 5448-5468, 3337-3357, 5415-5435, 3340-3360, 3318-3338, 5207-5227, 1812-1832, 5409-5429, 4629-4649, 4628-4648, 3344-3364, 1809-1829, 5443-5463, 3244-3264, 3180-3200, 3327-3347, 4522-4542, 2667-2687, 4668-4688, 4083-4103, 5445-5465, 2294-2314, 4842-4862, 5438-5458, 4084-4104, 2668-2688, 4526-4546, 4521-4541, 5459-5479, 3188-3208, 5467-5487, 5441-5461, 4519-4539, 4669-4689, 5450-5470, 3341-3361, 5458-5478, 4520-4540, 4329-4349, 4525-4545, 4524-4544, 5208-5228, 5305-5325, 4475-4495, 2666-2686, 4086-4106, 4523-4543, 4527-4547, 4085-4105, 5259-5279, 518-540, 519-541, 5462-5484, 1811-1833, 2376-2398, 3240-3262, 5440-5462, 1663-1685, 1814-1836, 4665-4687, 3181-3203, 3420-3442, 3324-3346, 2377-2399, 3336-3358, 5444-5466, 5438-5460, 5408-5430, 3244-3266, 3179-3201, 2295-2317, 2378-2400, 3326-3348, 5458-5480, 3182-3204, 3418-3440, 3319-3341, 4527-4549, 5471-5493, 5464-5486, 5437-5459, 5367-5389, 4526-4548, 4668-4690, 3419-3441, 2296-2318, 5442-5464, 5446-5468, 3335-3357, 5413-5435, 3338-3360, 3316-3338, 1810-1832, 5407-5429, 4627-4649, 4626-4648, 3342-3364, 1807-1829, 5441-5463, 3242-3264, 3178-3200, 3325-3347, 4520-4542, 2665-2687, 4666-4688, 4081-4103, 5443-5465, 2292-2314, 4840-4862, 5436-5458, 4082-4104, 2666-2688, 4524-4546, 4519-4541, 5457-5479, 3186-3208, 5465-5487, 5439-5461, 4517-4539, 4667-4689, 5448-5470, 3339-3361, 5456-5478, 4518-4540, 4327-4349, 4523-4545, 4522-4544, 5206-5228, 5303-5325, 4473-4495, 2664-2686, 4084-4106, 4521-4543, 4525-4547, 4083-4105, and 5257-5279 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 520-540, 524-544, 521-541, 5207-5227, 4670-4690, 3420-3440, 3328-3348, 1665-1685, 5409-5429, 5439-5459, 4527-4547, 5441-5461, 5410-5430, 5446-5466, 5467-5487, 5369-5389, 3421-3441, 5442-5462, 2379-2399, 4715-4735, 5464-5484, 3244-3264, 5440-5460, 1812-1832, 3181-3201, 3327-3347, 5448-5468, 4529-4549, 2378-2398, 4668-4688, 5438-5458, 5465-5485, 3326-3346, 3180-3200, 5458-5478, 3321-3341, 3338-3358, 3188-3208, 2294-2314, 4628-4648, 5415-5435, 5459-5479, 3184-3204, 2375-2395, 3422-3442, 3246-3266, 3337-3357, 2297-2317, 4528-4548, 3183-3203, 5450-5470, 5444-5464, 5466-5486, 2380-2400, 3242-3262, 4520-4540, 5445-5465, 3318-3338, 1816-1836, 5443-5463, 5460-5480, 4842-4862, 3338-3358, 1809-1829, 3423-3443, 4720-4740, 5259-5279, 4084-4104, 1813-1833, 4522-4542, 4822-4842, 4523-4543, 2298-2318, 4521-4541, 4086-4106, 4524-4544, 2668-2688, 4667-4687, 4083-4103, 4085-4105, 4629-4649, 4329-4349, 2667-2687, 4475-4495, 3344-3364, 4669-4689, 3340-3360, 4519-4539, 2666-2686, 5208-5228, 4526-4546, 4525-4545, 3341-3361, 518-540, 522-544, 519-541, 4668-4690, 3418-3440, 3326-3348, 1663-1685, 5407-5429, 5437-5459, 4525-4547, 5439-5461, 5408-5430, 5444-5466, 5465-5487, 5367-5389, 3419-3441, 5440-5462, 2377-2399, 4713-4735, 5462-5484, 3242-3264, 5438-5460, 1810-1832, 3179-3201, 3325-3347, 5446-5468, 4527-4549, 2376-2398, 4666-4688, 5436-5458, 5463-5485, 3324-3346, 3178-3200, 5456-5478, 3319-3341, 3336-3358, 3186-3208, 2292-2314, 4626-4648, 5413-5435, 5457-5479, 3182-3204, 2373-2395, 3420-3442, 3244-3266, 3335-3357, 2295-2317, 4526-4548, 3181-3203, 5448-5470, 5442-5464, 5464-5486, 2378-2400, 3240-3262, 4518-4540, 5443-5465, 3316-3338, 1814-1836, 5441-5463, 5458-5480, 4840-4862, 1807-1829, 3421-3443, 4718-4740, 5257-5279, 4082-4104, 1811-1833, 4520-4542, 4820-4842, 4521-4543, 2296-2318, 4519-4541, 4084-4106, 4522-4544, 2666-2688, 4665-4687, 4081-4103, 4083-4105, 4627-4649, 4327-4349, 2665-2687, 4473-4495, 3342-3364, 4667-4689, 3338-3360, 4517-4539, 2664-2686, 5206-5228, 4524-4546, 4523-4545, and 3339-3361 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 977-997, 980-1000, 973-993, 988-1008, 987-1007, 972-992, 979-999, 1001-1021, 976-996, 994-1014, 1002-1022, 978-998, 974-994, 520-540, 521-541, 5464-5484, 1813-1833, 2378-2398, 3242-3262, 5442-5462, 1665-1685, 524-544, 5207-5227, 4670-4690, 3420-3440, 3328-3348, 5409-5429, 5439-5459, 4527-4547, 5441-5461, 5410-5430 and 5446-5466 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 3 selected from the group of nucleotides 512-532, 513-533, 514-534, 515-535, 516-536, 517-537, 518-538, 519-539, 520-540, 1063-1083, 1067-1087, 1072-1092, 1074-1094, 1075-1095, 1125-1145, 1126-1146, 1127-1147, 1129-1149, 1170-1190, 1395-1415, 1905-1925, 1906-1926, 1909-1929, 1911-1931, 1912-1932, 1913-1933, 1914-1934, 1915-1935, 1916-1936, 1919-1939, 1951-1971, 1954-1974, 1958-1978, 2387-2407, 2409-2429, 2410-2430, 2469-2489, 2471-2491, 2472-2492, 2476-2496, 2477-2497, 2478-2498, 2480-2500, 2481-2501, 2482-2502, 2484-2504, 2762-2782, 2764-2784, 2766-2786, 2767-2787, 2768-2788, 2769-2789, 2819-2839, 2821-2841, 2828-2848, 2943-2963, 2944-2964, 2946-2966, 2947-2967, 3252-3272, 3277-3297, 3280-3300, 3281-3301, 3282-3302, 3284-3304, 3285-3305, 3286-3306, 3331-3351, 3332-3352, 3333-3353, 3334-3354, 3335-3355, 3336-3356, 3338-3358, 3340-3360, 3342-3362, 3343-3363, 3344-3364, 3345-3365, 3346-3366, 3347-3367, 3349-3369, 3350-3370, 3353-3373, 3364-3384, 3366-3386, 3367-3387, 3368-3388, 3369-3389, 3370-3390, 3412-3432, 3414-3434, 3415-3435, 3416-3436, 3417-3437, 3419-3439, 3420-3440, 3424-3444, 3425-3445, 3426-3446, 3427-3447, 3428-3448, 3429-3449, 3430-3450, 3431-3451, 3434-3454, 4132-4152, 4134-4154, 4179-4199, 4182-4202, 4184-4204, 4395-4415, 4425-4445, 4426-4446, 4429-4449, 4469-4489, 4470-4490, 4471-4491, 4472-4492, 4473-4493, 4474-4494, 4569-4589, 4571-4591, 4572-4592, 4596-4616, 4623-4643, 4721-4741, 4722-4742, 4725-4745, 4726-4746, 4766-4786, 4767-4787, 4768-4788, 4769-4789, 4770-4790, 4779-4799, 4805-4825, 4806-4826, 4807-4827, 4808-4828, 4809-4829, 4812-4832, 4813-4833, 4814-4834, 4936-4956, 5072-5092, 5073-5093, 5345-5365, 5346-5366, 5349-5369, 5350-5370, 5351-5371, 5460-5480, 5461-5481, 5463-5483, 5465-5485, 5467-5487, 5468-5488, 5469-5489, 5470-5490, 5471-5491, 5505-5525, 5506-5526, 5507-5527, 5508-5528, 5509-5529, 5511-5531, 5513-5533, 5514-5534, 5541-5561, 5544-5564, 5546-5566, 5547-5567, 5548-5568, 5550-5570, 5551-5571, 5574-5594, 5576-5596, 5614-5634, 521-541, 522-542, 523-543, 524-544, 525-545, 526-546, 527-547, 528-548, 529-549, 530-550, 531-551, 532-552, 533-553, 534-554, 535-555, 536-556, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063, 1044-1064, 1045-1065, 1046-1066, 1047-1067, 1048-1068, 1049-1069, 1050-1070, 1051-1071, 1052-1072, 1053-1073, 1054-1074, 1062-1082, 1064-1084, 1065-1085, 1066-1086, 1068-1088, 1069-1089, 1070-1090, 1071-1091, 1073-1093, 1076-1096, 1077-1097, 1078-1098, 1079-1099, 1080-1100, 1081-1101, 1082-1102, 1128-1148, 1129-1149, 1130-1150, 1131-1151, 1132-1152, 1133-1153, 1134-1154, 1135-1155, 1136-1156, 1137-1157, 1138-1158, 1139-1159, 1140-1160, 1141-1161, 1142-1162, 1143-1163, 1144-1164, 1145-1165, 1146-1166, 1147-1167, 1148-1168, 975-995, 976-996, 977-997, 978-998, 979-999, 980-1000, 981-1001, 982-1002, 983-1003, 984-1004, 985-1005, 986-1006, 987-1007, 988-1008, 989-1009, 990-1010, 991-1011, 992-1012, 993-1013, 994-1014, 995-1015, 996-1016, 997-1017, 998-1018, 999-1019, 1000-1020, 1001-1021, 1002-1022, 1003-1023, 1004-1024, 1005-1025, 1006-1026, 1007-1027, 1008-1028, 1009-1029, 1010-1030, 1011-1031, 1012-1032, 1013-1033, 1014-1034, 1015-1035, 1016-1036, 1017-1037, 1018-1038, 1019-1039, 1020-1040, 1021-1041, 1022-1042, 1023-1043, 1024-1044, 1025-1045, 1026-1046, 1027-1047, 1028-1048, 1029-1049, 1030-1050, 1031-

1051, 1032-1052, 1033-1053, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063 and 1045-1065 of SEQ ID NO: 3, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 5 selected from the group of nucleotides 1065-1085, 1195-1215, 1066-1086, 1068-1088, 705-725, 1067-1087, 4520-4540, 3341-3361, 4515-4535, 5284-5304, 5285-5305, 344-364, 5283-5303, 5354-5374, 2459-2479, 1061-1081, 706-726, 972-992, 4564-4584, 995-1015, 4546-4566, 968-988, 1127-1147, 4534-4554, 158-178, 4494-4514, 1691-1711, 3544-3564, 198-218, 979-999, 4548-4568, 4551-4571, 543-563, 715-735, 542-562, 352-372, 362-382, 4556-4576, 4547-4567, 4542-4562, 4558-4578, 4549-4569, 5074-5094, 4552-4572, 5073-5093, 5076-5096, 4550-4570 and 2753-2773 of SEQ ID NO: 5, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target MAPT sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 3-8, 12-13, and 16-28, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 3-8, 12-13, and 16-28, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target MAPT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 1, 3, 5, 7, 9 and 11, or a fragment of any one of SEQ ID NOs: 1, 3, 5, 7, 9 and 11, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary. In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target MAPT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of Tables 3-8, 12-13, and 16-28, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 3-8, and 16-28, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In certain embodiments, the sense and antisense strands are selected from any one of duplexes AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-523803.1, AD-523817.1, AD-523825.1, AD-523811.1, AD-523854.1, AD-523797.1, AD-523805.1, AD-523814.1, AD-523804.1, AD-1019356.1, AD-523846.1, AD-523808.1, AD-523835.1, AD-1019357.1, AD-523853.1, AD-523819.1, AD-523830.1, AD-523834.1, AD-523850.1, AD-523820.1, AD-523849.1, AD-523845.1, AD-393758.3, AD-523848.1, AD-523840.1, AD-523828.1, AD-523822.1, AD-523806.1, AD-523831.1, AD-393757.1, AD-523839.1, AD-523815.1, AD-523856.1, AD-1019330.1, AD-523829.1, AD-523855.1, AD-523836.1, AD-1019329.1, AD-523843.1, AD-523807.1, AD-523821.1, AD-523826.1, AD-523847.1, AD-523786.1, AD-523812.1, AD-523827.1, AD-523844.1, AD-523851.1, AD-523818.1, AD-523832.1, AD-523813.1, AD-523841.1, AD-1019352.1, AD-1019354.1, AD-523852.1, AD-523842.1, AD-523833.1, AD-1019328.1, AD-1019355.1, AD-1019353.1, AD-1019350.1 and AD-1019351.1. In particular embodiments, the sense and antisense strands are selected from any one of duplexes AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1 and AD-523796.1.

In certain embodiments, the sense and antisense strands are selected from any one of duplexes AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-535925.1, AD-538012.1, AD-536872.1, AD-536954.1, AD-536964.1, AD-536318.1, AD-536976.1, AD-538630.1, AD-538624.1, AD-538594.1, AD-536915.1, AD-536870.1, AD-536236.1, AD-536319.1, AD-536966.1, AD-538643.1, AD-536873.1, AD-536952.1, AD-536959.1, AD-537921.1, AD-538652.1, AD-538649.1, AD-538623.1, AD-538573.1, AD-537920.1, AD-536939.1, AD-538015.1, AD-536953.1, AD-536237.1, AD-538628.1, AD-538632.1, AD-536975.1, AD-538599.1, AD-536978.1, AD-536956.1, AD-538571.1, AD-535921.1, AD-538593.1, AD-537974.1, AD-537973.1, AD-536982.1, AD-535918.1, AD-538627.1, AD-536913.1, AD-536869.1, AD-536965.1, AD-537914.1, AD-536504.1, AD-538013.1, AD-537579.1, AD-538629.1, AD-536233.1, AD-538141.1, AD-538622.1, AD-537580.1, AD-536505.1, AD-537918.1, AD-537913.1, AD-538642.1, AD-536877.1, AD-538650.1, AD-538625.1, AD-537911.1, AD-538014.1, AD-538634.1, AD-536979.1, AD-538641.1, AD-537912.1, AD-537761.1, AD-537917.1, AD-537916.1, AD-538432.1, AD-538529.1, AD-537867.1, AD-536503.1, AD-537582.1, AD-537915.1, AD-537919.1, AD-537581.1 and AD-538483.1. In particular embodiments, the sense and antisense strands are selected from any one of duplexes AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1 and AD-535864.1.

In certain embodiments, the sense and antisense strands are selected from any one of duplexes AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1, AD-526993.1, AD-527013.1, AD-526936.1, AD-395453.1, AD-526989.1, AD-524719.1, AD-526423.1, AD-527010.1, AD-525305.1, AD-526987.1, AD-524331.1, AD-525266.1, AD-525342.1,

AD-526995.1, AD-526298.1, AD-524718.1, AD-526392.1, AD-526985.1, AD-527011.1, AD-525341.1, AD-525265.1, AD-527004.1, AD-525336.1, AD-525353.1, AD-525273.1, AD-524638.1, AD-526350.1, AD-526962.1, AD-527005.1, AD-525269.1, AD-524715.1, AD-395454.1, AD-525307.1, AD-525352.1, AD-524641.1, AD-526297.1, AD-525268.1, AD-526997.1, AD-526991.1, 5 AD-527012.1, AD-524720.1, AD-525303.1, AD-526289.1, AD-526992.1, AD-525333.1, AD-524335.1, AD-526990.1, AD-527006.1, AD-526505.1, AD-525309.1, AD-524328.1, AD-395455.1, AD-526428.1, AD-526847.1, AD-525957.1, AD-524332.1, AD-526291.1, AD-526485.1, AD-526292.1, AD-524642.1, AD-526290.1, AD-525959.1, AD-526293.1, AD-524899.1, AD-526391.1, AD-525956.1, AD-525958.1, AD-526351.1, AD-526138.1, AD-524898.1, AD-526244.1, AD-10 525359.1, AD-526393.1, AD-525355.1, AD-526288.1, AD-524897.1, AD-526796.1, AD-526295.1, AD-526294.1 and AD-525356.1. In particular embodiments, the sense and antisense strands are selected from any one of duplexes AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1, and AD-526993.1.

15 In certain embodiments, the sense and antisense strands are selected from any one of duplexes AD-393758.1, AD-393888.1, AD-393759.1, AD-393761.1, AD-393495.1, AD-393760.1, AD-396425.1, AD-395441.1, AD-396420.1, AD-397103.1, AD-397104.1, AD-393239.1, AD-397102.1, AD-397167.1, AD-394791.1, AD-393754.1, AD-393496.1, AD-393667.1, AD-396467.1, AD-393690.1, AD-396449.1, AD-393663.1, AD-393820.1, AD-396437.1, AD-393084.1, AD-396401.1, 20 AD-394296.1, AD-395574.1, AD-393124.1, AD-393674.1, AD-396451.1, AD-396454.1, AD-393376.1, AD-393505.1, AD-393375.1, AD-393247.1, AD-393257.1, AD-396459.1, AD-396450.1, AD-396445.1, AD-396461.1, AD-396452.1, AD-396913.1, AD-396455.1, AD-396912.1, AD-396915.1, AD-396453.1 and AD-394991.1.

In one embodiment, the sense and antisense strands are selected from any one of duplexes 25 AD-1397070.1, AD-1397070.2, AD-1397071.1, AD-1397071.2, AD-1397072.1, AD-1397072.2, AD-1397073.1, AD-1397073.2, AD-1397074.1, AD-1397074.2, AD-1397075.1, AD-1397075.2, AD-1397076.1, AD-1397076.2, AD-1397077.1, AD-1397077.2, AD-1397078.1, AD-1397078.2, AD-1397250.1, AD-1397251.1, AD-1397252.1, AD-1397253.1, AD-1397254.1, AD-1397255.1, AD-1397256.1, AD-1397257.1, AD-1397258.1, AD-1397259.1, AD-1397260.1, AD-1397261.1, AD-30 1397262.1, AD-1397263.1, AD-1397264.1, AD-1397265.1, AD-1423242.1, AD-1423243.1, AD-1423244.1, AD-1423245.1, AD-1423246.1, AD-1423247.1, AD-1423248.1, AD-1423249.1, AD-1423250.1, AD-1423251.1, AD-1423252.1, AD-1423253.1, AD-1423254.1, AD-1423255.1, AD-1423256.1, AD-1423257.1, AD-1423258.1, AD-1423259.1, AD-1423260.1, AD-1423261.1, AD-1423262.1, AD-1423263.1, AD-1423264.1, AD-1423265.1, AD-1423266.1, AD-1423267.1, AD-35 1423268.1, AD-1423269.1, AD-1423270.1, AD-1423271.1, AD-1423272.1, AD-1423273.1, AD-1423274.1, AD-1423275.1, AD-1423276.1, AD-1423277.1, AD-1423278.1, AD-1423279.1, AD-1423280.1, AD-1423281.1, AD-1423282.1, AD-1423283.1, AD-1423284.1, AD-1423285.1, AD-1423286.1, AD-1423287.1, AD-1423288.1, AD-1423289.1, AD-1423290.1, AD-1423291.1, AD-1423292.1, AD-1423293.1, AD-1423294.1, AD-1423295.1, AD-1423296.1, AD-1423297.1, AD-

1423298.1, AD-1423299.1, AD-1423300.1, AD-1397266.1, AD-1397266.2, AD-1397267.1, AD-1423301.1, AD-1397268.1, AD-1397268.2, AD-1397269.1, AD-1423302.1, AD-1397270.1, AD-1397270.2, AD-1397271.1, AD-1397271.2, AD-1397272.1, AD-1423303.1, AD-1397273.1, AD-1423304.1, AD-1397274.1, AD-1423305.1, AD-1397275.1, AD-1423306.1, AD-1397276.1, AD-1397277.1, AD-1397277.2, AD-1397278.1, AD-1397279.1, AD-1397280.1, AD-1397281.1, AD-1397282.1, AD-1397283.1, AD-1397284.1, AD-1397285.1, AD-1397286.1, AD-1397287.1, AD-1397079.1, AD-1397079.2, AD-1397288.1, AD-1397289.1, AD-1397290.1, AD-1397080.1, AD-1397080.2, AD-1397291.1, AD-1397292.1, AD-1397293.1, AD-1397294.1, AD-1397081.1, AD-1397081.2, AD-1397295.1, AD-1397082.1, AD-1397082.2, AD-1397083.1, AD-1397083.2, AD-1397296.1, AD-1397297.1, AD-1397298.1, AD-1397299.1, AD-1397300.1, AD-1397301.1, AD-1397302.1, AD-1397084.1, AD-1397085.1, AD-1397086.1, AD-1397303.1, AD-1397087.1, AD-1397087.2, AD-1397304.1, AD-1397305.1, AD-1397306.1, AD-1397307.1, AD-1397308.1, AD-1397309.1, AD-1397310.1, AD-1397311.1, AD-1397312.1, AD-1397313.1, AD-1397314.1, AD-1397315.1, AD-1397316.1, AD-1397317.1, AD-1397318.1, AD-1397319.1, AD-1397320.1, AD-1397321.1, AD-1397322.1, AD-1397088.1, AD-1397089.1, AD-1397090.1, AD-1397091.1, AD-1397092.1, AD-1397093.1, AD-1397094.1, AD-1397095.1, AD-1397096.1, AD-1397097.1, AD-1397098.1, AD-1397099.1, AD-1397101.1, AD-1397102.1, AD-1397103.1, AD-1397104.1, AD-1397105.1, AD-1397106.1, AD-1397107.1, AD-1397108.1, AD-1397109.1, AD-1397110.1, AD-1397111.1, AD-1397112.1, AD-1397113.1, AD-1397114.1, AD-1397115.1, AD-1397116.1, AD-1397117.1, AD-1397118.1, AD-1397119.1, AD-1397120.1, AD-1397121.1, AD-1397122.1, AD-1397123.1, AD-1397124.1, AD-1397125.1, AD-1397126.1, AD-1397127.1, AD-1397128.1, AD-1397129.1, AD-1397130.1, AD-1397131.1, AD-1397132.1, AD-1397133.1, AD-1397134.1, AD-1397135.1, AD-1397136.1, AD-1397137.1, AD-1397138.1, AD-1397139.1, AD-1397140.1, AD-1397141.1, AD-1397142.1, AD-1397143.1, AD-1397144.1, AD-1397145.1, AD-1397146.1, AD-1397147.1, AD-1397148.1, AD-1397149.1, AD-1397150.1, AD-1397151.1, AD-1397152.1, AD-1397153.1, AD-1397154.1, AD-1397155.1, AD-1397156.1, AD-1397157.1, AD-1397158.1, AD-1397159.1, AD-1397160.1, AD-1397161.1, AD-1397162.1, AD-1397163.1, AD-1397164.1, AD-1397165.1, AD-1397166.1, AD-1397167.1, AD-1397168.1, AD-1397169.1, AD-1397170.1, AD-1397171.1, AD-1397172.1, AD-1397173.1, AD-1397174.1, AD-1397175.1, AD-1397176.1, AD-1397177.1, AD-1397178.1, AD-1397179.1, AD-1397180.1, AD-1397181.1, AD-1397182.1, AD-1397183.1, AD-1397184.1, AD-1397185.1, AD-1397186.1, AD-1397187.1, AD-1397188.1, AD-1397189.1, AD-1397190.1, AD-1397191.1, AD-1397192.1, AD-1397193.1, AD-1397194.1, AD-1397195.1, AD-1397196.1, AD-1397197.1, AD-1397198.1, AD-1397199.1, AD-1397200.1, AD-1397201.1, AD-1397202.1, AD-1397203.1, AD-1397204.1, AD-1397205.1, AD-1397206.1, AD-1397207.1, AD-1397208.1, AD-1397209.1, AD-1397210.1, AD-1397211.1, AD-1397212.1, AD-1397213.1, AD-1397214.1, AD-1397215.1, AD-1397216.1, AD-1397217.1, AD-1397218.1, AD-1397219.1, AD-1397220.1, AD-1397221.1, AD-1397222.1, AD-1397223.1, AD-1397224.1, AD-1397225.1, AD-1397226.1, AD-1397227.1, AD-1397228.1, AD-1397229.1, AD-1397230.1, AD-1397231.1, AD-1397232.1, AD-1397233.1, AD-1397234.1, AD-1397235.1, AD-1397236.1, AD-

1397237.1, AD-1397238.1, AD-1397239.1, AD-1397240.1, AD-1397241.1, AD-1397242.1, AD-1397243.1, AD-1397244.1, AD-1397245.1, AD-1397246.1, AD-1397247.1, AD-1397248.1, AD-1397249.1, AD-523565.1, AD-1397072.3, AD-1397073.3, AD-1397076.3, AD-1397077.3, AD-1397078.3, AD-1397252.2, AD-1397257.2, AD-1397258.2, AD-1397259.2, AD-1397263.2, AD-1397264.2, AD-1397309.2, AD-64958.114, AD-393758.4, AD-1397080.3, AD-1397293.2, AD-1397294.2, AD-1397081.3, AD-1397083.3, AD-1397298.2, AD-1397299.2, AD-1397084.2, AD-1397085.2, AD-1397087.3, AD-1397306.2, AD-1397307.2, AD-1397308.2 and AD-1397088.2.

In one embodiment, at least partial suppression of the expression of a MAPT gene, is assessed by a reduction of the amount of MAPT mRNA, *e.g.*, sense mRNA, antisense mRNA, total MAPT mRNA, which can be isolated from or detected in a first cell or group of cells in which a MAPT gene is transcribed and which has or have been treated such that the expression of a MAPT gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells). The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \times 100$$

The phrase “contacting a cell with an RNAi agent,” such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the RNAi agent or contacting a cell *in vivo* with the RNAi agent. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, the central nervous system (CNS), optionally *via* intrathecal, intravitreal, intracisternal or other injection, or to the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the RNAi agent may contain or be coupled to a ligand, *e.g.*, a lipophilic moiety or moieties as described below and further detailed, *e.g.*, in PCT/US2019/031170, which is incorporated herein by reference, that directs or otherwise stabilizes the RNAi agent at a site of interest, *e.g.*, the CNS. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

In one embodiment, contacting a cell with an RNAi agent includes “introducing” or “delivering the RNAi agent into the cell” by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an RNAi agent can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an RNAi agent into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, an RNAi agent can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell includes methods known in the art such as

electroporation and lipofection. Further approaches are described herein below or are known in the art.

The term “lipophile” or “lipophilic moiety” broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, $\log K_{ow}$, where K_{ow} is the ratio of a chemical's concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko et al., *J. Chem. Inf. Comput. Sci.* 41:1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (*i.e.* its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its $\log K_{ow}$ exceeds 0. Typically, the lipophilic moiety possesses a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10. For instance, the $\log K_{ow}$ of 6-amino hexanol, for instance, is predicted to be approximately 0.7. Using the same method, the $\log K_{ow}$ of cholesteryl N-(hexan-6-ol) carbamate is predicted to be 10.7.

The lipophilicity of a molecule can change with respect to the functional group it carries. For instance, adding a hydroxyl group or amine group to the end of a lipophilic moiety can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the lipophilic moiety.

Alternatively, the hydrophobicity of the double-stranded RNAi agent, conjugated to one or more lipophilic moieties, can be measured by its protein binding characteristics. For instance, in certain embodiments, the unbound fraction in the plasma protein binding assay of the double-stranded RNAi agent could be determined to positively correlate to the relative hydrophobicity of the double-stranded RNAi agent, which could then positively correlate to the silencing activity of the double-stranded RNAi agent.

In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. An exemplary protocol of this binding assay is illustrated in detail in, *e.g.*, PCT/US2019/031170. Briefly, duplexes were incubated with human serum albumin and the unbound fraction was determined. Exemplary assay protocol includes duplexes at a stock concentration of 10 μ M, diluted to a final concentration of 0.5 μ M (20 μ L total volume) containing 0, 20, or 90% serum in 1x PBS. The samples can be mixed, centrifuged for 30 seconds, and subsequently incubated at room temperature for 10 minutes. Once incubation step is completed, 4 μ L of 6x EMSA Gel-loading solution can be added to each sample, centrifuged for 30 seconds, and 12 μ L of each sample can be loaded onto a 26 well BioRad 10% PAGE (polyacrylamide gel electrophoresis). The gel can be run for 1 hour at 100 volts. After completion of the run, the gel is removed from the casing and washed in 50 mL of 10% TBE (Tris base, boric acid and EDTA). Once washing is complete, 5 μ L of SYBR Gold can be added to the gel, which is then allowed to incubate at room temperature for 10 minutes, and the gel-washed again in 50 mL of 10% TBE. In this

exemplary assay, a Gel Doc XR+ gel documentation system may be used to read the gel using the following parameters: the imaging application set to SYBR Gold, the size set to Bio-Rad criterion gel, the exposure set to automatic for intense bands, the highlight saturated pixels may be turned one and the color is set to gray. The detection, molecular weight analysis, and output can all disabled. Once a
5 clean photo of the gel is obtained Image Lab 5.2 may be used to process the image. The lanes and bands can be manually set to measure band intensity. Band intensities of each sample can be normalized to PBS to obtain the fraction of unbound siRNA. From this measurement relative hydrophobicity can determined. The hydrophobicity of the double-stranded RNAi agent, measured by fraction of unbound siRNA in the binding assay, exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds
10 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

Accordingly, conjugating the lipophilic moieties to the internal position(s) of the double-stranded RNAi agent provides optimal hydrophobicity for the enhanced *in vivo* delivery of siRNA.

The term “lipid nanoparticle” or “LNP” is a vesicle comprising a lipid layer encapsulating a
15 pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.*, a RNAi agent or a plasmid from which an RNAi agent is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, a “subject” is an animal, such as a mammal, including a primate (such as a
20 human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), or a non-primate (such as a rat, or a mouse). In a preferred embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder, or condition that would benefit from reduction in MAPT expression; a human at risk for a disease, disorder, or condition that would benefit from reduction in MAPT expression; a human having a disease, disorder, or condition that would benefit from reduction in MAPT
25 expression; or human being treated for a disease, disorder, or condition that would benefit from reduction in MAPT expression as described herein. In some embodiments, the subject is a female human. In other embodiments, the subject is a male human. In one embodiment, the subject is an adult subject. In one embodiment, the subject is a pediatric subject. In another embodiment, the subject is a juvenile subject, *i.e.*, a subject below 20 years of age.

30 As used herein, the terms “treating” or “treatment” refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more signs or symptoms associated with MAPT gene expression or Tau production in MAPT-associated diseases, such as Alzheimer’s disease, FTD, PSP, or other tauopathies. “Treatment” can also mean prolonging survival as compared to expected survival in the absence of treatment.

35 The term “lower” in the context of the level of MAPT in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, *e.g.*, the level of sense- or antisense-containing foci

and/or the level of aberrant dipeptide repeat protein, *e.g.*, a decrease of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In some embodiments, a decrease is at least about 25% in a disease marker, *e.g.*, Tau protein and/or gene expression level is decreased by, *e.g.*, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% “Lower” in the context of the level of MAPT in a subject is preferably down to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, “lower” is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual, *e.g.*, the level of decrease in bodyweight between an obese individual and an individual having a weight accepted within the range of normal.

As used herein, “prevention” or “preventing,” when used in reference to a disease, disorder, or condition thereof, that would benefit from a reduction in expression of a MAPT gene or production of a Tau, refers to a reduction in the likelihood that a subject will develop a symptom associated with such a disease, disorder, or condition, *e.g.*, a symptom of a MAPT-associated disease. The failure to develop a disease, disorder, or condition, or the reduction in the development of a symptom associated with such a disease, disorder, or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

As used herein, the term “MAPT-associated disease” or “MAPT-associated disorder” or “tauopathy” includes any disease or disorder that would benefit from reduction in the expression and/or activity of MAPT. Exemplary MAPT-associated diseases include Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick’s disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson’s disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

“Therapeutically effective amount,” as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a MAPT-associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The “therapeutically effective amount” may vary depending on the RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

“Prophylactically effective amount,” as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a MAPT-associated disorder, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The

5 “prophylactically effective amount” may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A “therapeutically-effective amount” or “prophylactically effective amount” also includes an

10 amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. An RNAi agent employed in the methods of the present disclosure may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds,

15 materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “pharmaceutically-acceptable carrier” as used herein means a pharmaceutically-

20 acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the

25 subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and

30 suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered

35 solutions; (21) polyesters, polycarbonates or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

The term “sample,” as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of

biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the brain
 5 (e.g., whole brain or certain segments of brain, e.g., striatum, or certain types of cells in the brain, such as, e.g., neurons and glial cells (astrocytes, oligodendrocytes, microglial cells)). In some embodiments, a “sample derived from a subject” refers to blood drawn from the subject or plasma or serum derived therefrom. In further embodiments, a “sample derived from a subject” refers to brain tissue (or subcomponents thereof) or retinal tissue (or subcomponents thereof) derived from the
 10 subject.

The term “substituted” refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: alkyl, alkenyl, alkynyl, aryl, heterocyclyl, halo, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl,
 15 arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent can be further substituted.

The term “alkyl” refers to saturated and unsaturated non-aromatic hydrocarbon chains that may be a straight chain or branched chain, containing the indicated number of carbon atoms (these include without limitation propyl, allyl, or propargyl), which may be optionally inserted with N, O, or S. For example, “(C1-C6) alkyl” means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement. “(C1-C6) alkyl” includes, for example, methyl, ethyl, propyl, iso-propyl, n-
 25 butyl, tert-butyl, pentyl and hexyl. In certain embodiments, a lipophilic moiety of the instant disclosure can include a C6-C18 alkyl hydrocarbon chain.

The term “alkylene” refers to an optionally substituted saturated aliphatic branched or straight chain divalent hydrocarbon radical having the specified number of carbon atoms. For example, “(C1-C6) alkylene” means a divalent saturated aliphatic radical having from 1-6 carbon atoms in a linear
 30 arrangement, e.g., $[(CH_2)_n]$, where n is an integer from 1 to 6. “(C1-C6) alkylene” includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, “(C1-C6) alkylene” means a divalent saturated radical having from 1-6 carbon atoms in a branched arrangement, for example: $[(CH_2CH_2CH_2CH_2CH(CH_3))]$, $[(CH_2CH_2CH_2CH_2C(CH_3)_2)]$, $[(CH_2C(CH_3)_2CH(CH_3))]$, and the like. The term “alkylenedioxy” refers to a divalent species of the structure —O—R—O—, in
 35 which R represents an alkylene.

The term “mercapto” refers to an —SH radical. The term “thioalkoxy” refers to an —S—alkyl radical.

The term “halo” refers to any radical of fluorine, chlorine, bromine or iodine. “Halogen” and “halo” are used interchangeably herein.

As used herein, the term “cycloalkyl” means a saturated or unsaturated nonaromatic hydrocarbon ring group having from 3 to 14 carbon atoms, unless otherwise specified. For example, “(C3-C10) cycloalkyl” means a hydrocarbon radical of a (3-10)-membered saturated aliphatic cyclic hydrocarbon ring. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, methyl-
5 cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, etc. Cycloalkyls may include multiple spiro- or fused rings. Cycloalkyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, the term “alkenyl” refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least one carbon-carbon double bond, and having from 2 to 10 carbon atoms
10 unless otherwise specified. Up to five carbon-carbon double bonds may be present in such groups. For example, “C2-C6” alkenyl is defined as an alkenyl radical having from 2 to 6 carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, and cyclohexenyl. The straight, branched, or cyclic portion of the alkenyl group may contain double bonds and is optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency. The term
15 “cycloalkenyl” means a monocyclic hydrocarbon group having the specified number of carbon atoms and at least one carbon-carbon double bond.

As used herein, the term “alkynyl” refers to a hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, and containing at least one carbon-carbon triple bond. Up to 5 carbon-carbon triple bonds may be present. Thus, “C2-C6 alkynyl” means
20 an alkynyl radical having from 2 to 6 carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butynyl. The straight or branched portion of the alkynyl group may contain triple bonds as permitted by normal valency, and may be optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, “alkoxyl” or “alkoxy” refers to an alkyl group as defined above with the
25 indicated number of carbon atoms attached through an oxygen bridge. For example, “(C1-C3)alkoxy” includes methoxy, ethoxy and propoxy. For example, “(C1-C6)alkoxy”, is intended to include C1, C2, C3, C4, C5, and C6 alkoxy groups. For example, “(C1-C8)alkoxy”, is intended to include C1, C2, C3, C4, C5, C6, C7, and C8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo, s-pentoxo, n-heptoxo, and n-octoxo. “Alkylthio” means an alkyl radical attached through a sulfur linking atom. The terms
30 “alkylamino” or “aminoalkyl”, means an alkyl radical attached through an NH linkage. “Dialkylamino” means two alkyl radical attached through a nitrogen linking atom. The amino groups may be unsubstituted, monosubstituted, or di-substituted. In some embodiments, the two alkyl radicals are the same (e.g., N,N-dimethylamino). In some embodiments, the two alkyl radicals are
35 different (e.g., N-ethyl-N-methylamino).

As used herein, “aryl” or “aromatic” means any stable monocyclic or polycyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, tetrahydronaphthyl, indanyl, and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that

attachment is via the aromatic ring. Aryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency. The term “arylalkyl” or the term “aralkyl” refers to alkyl substituted with an aryl. The term “arylalkoxy” refers to an alkoxy substituted with aryl.

5 “Hetero” refers to the replacement of at least one carbon atom in a ring system with at least one heteroatom selected from N, S and O. “Hetero” also refers to the replacement of at least one carbon atom in an acyclic system. A hetero ring system or a hetero acyclic system may have, for example, 1, 2 or 3 carbon atoms replaced by a heteroatom.

As used herein, the term “heteroaryl” represents a stable monocyclic or polycyclic ring of up
10 to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Examples of heteroaryl groups include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, benzimidazolonyl, benzoxazolonyl, quinolinyl, isoquinolinyl, dihydroisindolonyl, imidazopyridinyl, isoindolonyl, indazolyl, oxazolyl, oxadiazolyl, isoxazolyl,
15 indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. “Heteroaryl” is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring. Heteroaryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as
20 permitted by normal valency.

As used herein, the term “heterocycle,” “heterocyclic,” or “heterocyclyl” means a 3- to 14-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, including polycyclic groups. As used herein, the term “heterocyclic” is also considered to be synonymous with the terms “heterocycle” and “heterocyclyl” and is
25 understood as also having the same definitions set forth herein. “Heterocyclyl” includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Examples of heterocyclyl groups include, but are not limited to, azetidiny, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl,
30 isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxooxazolidinyl, oxazolyl, oxazoline, oxopiperazinyl, oxopyrrolidinyl, oxomorpholinyl, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyridinonyl, pyrimidyl, pyrimidinonyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl,
35 thienyl, triazolyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl,

dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, dioxidothiomorpholinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom. Heterocyclyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

“Heterocycloalkyl” refers to a cycloalkyl residue in which one to four of the carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. Examples of heterocycles whose radicals are heterocyclyl groups include tetrahydropyran, morpholine, pyrrolidine, piperidine, thiazolidine, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like.

The term “heteroaryl” refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like. The term “heteroarylalkyl” or the term “heteroaralkyl” refers to an alkyl substituted with a heteroaryl. The term “heteroarylalkoxy” refers to an alkoxy substituted with heteroaryl.

The term “cycloalkyl” as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example, 3 to 8 carbons, and, for example, 3 to 6 carbons, wherein the cycloalkyl group additionally may be optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term “acyl” refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

As used herein, “keto” refers to any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, or aryl group as defined herein attached through a carbonyl bridge.

Examples of keto groups include, but are not limited to, alkanoyl (e.g., acetyl, propionyl, butanoyl, pentanoyl, hexanoyl), alkenoyl (e.g., acryloyl) alkynoyl (e.g., ethynoyl, propynoyl, butynoyl, pentynoyl, hexynoyl), aryloyl (e.g., benzoyl), heteroaryloyl (e.g., pyrroloyl, imidazoloyl, quinolinoyl, pyridinoyl).

As used herein, “alkoxycarbonyl” refers to any alkoxy group as defined above attached through a carbonyl bridge (i.e., —C(O)O-alkyl). Examples of alkoxycarbonyl groups include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, iso-propoxycarbonyl, n-propoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or n-pentoxycarbonyl.

As used herein, “aryloxycarbonyl” refers to any aryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-aryl). Examples of aryloxycarbonyl groups include, but are not limited to, phenoxycarbonyl and naphthyloxycarbonyl.

As used herein, “heteroaryloxycarbonyl” refers to any heteroaryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-heteroaryl). Examples of heteroaryloxycarbonyl groups include, but are not limited to, 2-pyridyloxycarbonyl, 2-oxazolyloxycarbonyl, 4-thiazolyloxycarbonyl, or pyrimidinylloxycarbonyl.

5 The term “oxo” refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

10 The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (e.g., N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which the compound or composition is placed. Accordingly, as used herein, the structures disclosed herein envisage that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover the disclosed compounds and compositions regardless of their state of protonation based on the pH of the environment, as would be readily understood by the person of ordinary skill in the art.

15

II. RNAi Agents of the Disclosure

Described herein are RNAi agents which inhibit the expression of a MAPT gene. In one embodiment, the RNAi agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a MAPT gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human having a MAPT-associated disease, *e.g.*, Alzheimer’s disease, FTD, PSP, or another tauopathy. The dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of a MAPT gene. The region of complementarity is about 15-30 nucleotides or less in length. Upon contact with a cell expressing the MAPT gene, the RNAi agent inhibits the expression of the MAPT gene (*e.g.*, a human gene, a primate gene, a non-primate gene) by at least 25%, or higher as described herein, when compared to a similar cell not contacted with the RNAi agent or an RNAi agent not complementary to the MAPT gene. Expression of the MAPT gene may be assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flowcytometric techniques. In one embodiment, the level of knockdown is assayed in BE (2)-C cells using an assay method provided in Example 1 below. In some embodiments, the level of knockdown is assayed in primary mouse hepatocytes. In some embodiments, the level of knockdown is assayed in Neuro-2a cells.

35 A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of a MAPT gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as

known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain preferred embodiments, the duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 basepairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In some embodiments, the duplex structure is 19 to 30 base pairs in length. Similarly, the region of complementarity to the target sequence is 19 to 30 nucleotides in length.

In some embodiments, the dsRNA is 15 to 23 nucleotides in length, 19 to 23 nucleotides in length, or 25 to 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well known in the art that dsRNAs longer than about 21-23 nucleotides can serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a "part" of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 15 to 36 base pairs, *e.g.*, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs, for example, 19-21 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a

dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an RNAi agent useful to target MAPT expression is not generated in the target cell by cleavage of a larger dsRNA.

5 A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs *e.g.*, 1, 2, 3, or 4 nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a
10 dsRNA.

A dsRNA can be synthesized by standard methods known in the art. Double stranded RNAi compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or
15 solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Similarly, single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In one aspect, a dsRNA of the disclosure includes at least two nucleotide sequences, a sense sequence and an antisense sequence. The sense strand sequence for MAPT may be selected from the group of
20 sequences provided in any one of Tables 3-8, 12-13, and 16-28, and the corresponding nucleotide sequence of the antisense strand of the sense strand may be selected from the group of sequences of any one of Tables 3-8, 12-13, and 16-28. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a
25 sequence of an mRNA generated in the expression of a MAPT gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 3-8, 12-13, and 16-28, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 3-8, 12-13, and 16-28.

30 In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 512-532, 513-533, 514-534, 515-535, 516-536, 517-537, 518-538, 519-539, 520-540, 1063-1083, 1067-1087, 1072-1092, 1074-1094, 1075-1095, 1125-1145, 1126-1146, 1127-1147, 1129-1149, 1170-1190, 1395-1415, 1905-1925, 1906-1926, 1909-1929, 1911-1931, 1912-1932, 1913-1933, 1914-1934, 1915-1935, 1916-
35 1936, 1919-1939, 1951-1971, 1954-1974, 1958-1978, 2387-2407, 2409-2429, 2410-2430, 2469-2489, 2471-2491, 2472-2492, 2476-2496, 2477-2497, 2478-2498, 2480-2500, 2481-2501, 2482-2502, 2484-2504, 2762-2782, 2764-2784, 2766-2786, 2767-2787, 2768-2788, 2769-2789, 2819-2839, 2821-2841, 2828-2848, 2943-2963, 2944-2964, 2946-2966, 2947-2967, 3252-3272, 3277-3297, 3280-3300, 3281-3301, 3282-3302, 3284-3304, 3285-3305, 3286-3306, 3331-3351, 3332-3352, 3333-3353, 3334-3354,

3335-3355, 3336-3356, 3338-3358, 3340-3360, 3342-3362, 3343-3363, 3344-3364, 3345-3365, 3346-3366, 3347-3367, 3349-3369, 3350-3370, 3353-3373, 3364-3384, 3366-3386, 3367-3387, 3368-3388, 3369-3389, 3370-3390, 3412-3432, 3414-3434, 3415-3435, 3416-3436, 3417-3437, 3419-3439, 3420-3440, 3424-3444, 3425-3445, 3426-3446, 3427-3447, 3428-3448, 3429-3449, 3430-3450, 3431-3451, 3434-3454, 4132-4152, 4134-4154, 4179-4199, 4182-4202, 4184-4204, 4395-4415, 4425-4445, 4426-4446, 4429-4449, 4469-4489, 4470-4490, 4471-4491, 4472-4492, 4473-4493, 4474-4494, 4569-4589, 4571-4591, 4572-4592, 4596-4616, 4623-4643, 4721-4741, 4722-4742, 4725-4745, 4726-4746, 4766-4786, 4767-4787, 4768-4788, 4769-4789, 4770-4790, 4779-4799, 4805-4825, 4806-4826, 4807-4827, 4808-4828, 4809-4829, 4812-4832, 4813-4833, 4814-4834, 4936-4956, 5072-5092, 5073-5093, 5345-5365, 5346-5366, 5349-5369, 5350-5370, 5351-5371, 5460-5480, 5461-5481, 5463-5483, 5465-5485, 5467-5487, 5468-5488, 5469-5489, 5470-5490, 5471-5491, 5505-5525, 5506-5526, 5507-5527, 5508-5528, 5509-5529, 5511-5531, 5513-5533, 5514-5534, 5541-5561, 5544-5564, 5546-5566, 5547-5567, 5548-5568, 5550-5570, 5551-5571, 5574-5594, 5576-5596, 5614-5634, 521-541, 522-542, 523-543, 524-544, 525-545, 526-546, 527-547, 528-548, 529-549, 530-550, 531-551, 532-552, 533-553, 534-554, 535-555, 536-556, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063, 1044-1064, 1045-1065, 1046-1066, 1047-1067, 1048-1068, 1049-1069, 1050-1070, 1051-1071, 1052-1072, 1053-1073, 1054-1074, 1062-1082, 1064-1084, 1065-1085, 1066-1086, 1068-1088, 1069-1089, 1070-1090, 1071-1091, 1073-1093, 1076-1096, 1077-1097, 1078-1098, 1079-1099, 1080-1100, 1081-1101, 1082-1102, 1128-1148, 1129-1149, 1130-1150, 1131-1151, 1132-1152, 1133-1153, 1134-1154, 1135-1155, 1136-1156, 1137-1157, 1138-1158, 1139-1159, 1140-1160, 1141-1161, 1142-1162, 1143-1163, 1144-1164, 1145-1165, 1146-1166, 1147-1167, 1148-1168, 975-995, 976-996, 977-997, 978-998, 979-999, 980-1000, 981-1001, 982-1002, 983-1003, 984-1004, 985-1005, 986-1006, 987-1007, 988-1008, 989-1009, 990-1010, 991-1011, 992-1012, 993-1013, 994-1014, 995-1015, 996-1016, 997-1017, 998-1018, 999-1019, 1000-1020, 1001-1021, 1002-1022, 1003-1023, 1004-1024, 1005-1025, 1006-1026, 1007-1027, 1008-1028, 1009-1029, 1010-1030, 1011-1031, 1012-1032, 1013-1033, 1014-1034, 1015-1035, 1016-1036, 1017-1037, 1018-1038, 1019-1039, 1020-1040, 1021-1041, 1022-1042, 1023-1043, 1024-1044, 1025-1045, 1026-1046, 1027-1047, 1028-1048, 1029-1049, 1030-1050, 1031-1051, 1032-1052, 1033-1053, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063 and 1045-1065 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

In certain embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 4 selected from the group of nucleotides, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 520-541, 520-556, 510-534, 512-536, 516-541, 516-540, 520-544, 524-547, 526-551, 529-556, 532-556, 1065-1089, 1068-1095, 1068-1094, 1075-1100, 1076-1100, 1079-1103, 1123-1147, 1127-1151, 1130-1155, 1903-1934, 1903-1930, 1914-1940, 1949-1975, 2470-2497, 2941-2965,

3275-3302, 3278-3302, 3329-3353, 3333-3357, 3338-3367, 3338-3366, 3348-3390, 3348-3388, 3351-3385, 5507-5562 and 5549-5597 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4. In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target MAPT sequence and comprise a contiguous nucleotide sequence complementary over its entire length to a fragment of SEQ ID NO: 4 selected from the group of nucleotides, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 520-541, 520-556, 510-534, 512-536, 516-541, 516-540, 520-544, 524-547, 526-551, 529-556, 532-556, 1065-1089, 1068-1095, 1068-1094, 1075-1100, 1076-1100, 1079-1103, 1123-1147, 1127-1151, 1130-1155, 1903-1934, 1903-1930, 1914-1940, 1949-1975, 2470-2497, 2941-2965, 3275-3302, 3278-3302, 3329-3353, 3333-3357, 3338-3367, 3338-3366, 3348-3390, 3348-3388, 3351-3385, 5507-5562 and 5549-5597 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 977-997, 980-1000, 973-993, 988-1008, 987-1007, 972-992, 979-999, 1001-1021, 976-996, 994-1014, 1002-1022, 978-998, 974-994, 520-540, 521-541, 5464-5484, 1813-1833, 2378-2398, 3242-3262, 5442-5462, 1665-1685, 524-544, 5207-5227, 4670-4690, 3420-3440, 3328-3348, 5409-5429, 5439-5459, 4527-4547, 5441-5461, 5410-5430 and 5446-5466 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1, AD-526993.1, AD-1397070.1, AD-1397070.2, AD-1397071.1, AD-1397071.2, AD-1397072.1, AD-1397072.2, AD-1397073.1, AD-1397073.2, AD-1397074.1, AD-1397074.2, AD-1397075.1, AD-1397075.2, AD-1397076.1, AD-1397076.2, AD-1397077.1, AD-1397077.2, AD-1397078.1, AD-1397078.2, AD-1397250.1, AD-1397251.1, AD-1397252.1, AD-1397253.1, AD-1397254.1, AD-1397255.1, AD-1397256.1, AD-1397257.1, AD-1397258.1, AD-1397259.1, AD-1397260.1, AD-1397261.1, AD-1397262.1, AD-1397263.1, AD-1397264.1, AD-1397265.1, AD-1423242.1, AD-1423243.1, AD-1423244.1, AD-1423245.1, AD-1423246.1, AD-1423247.1, AD-1423248.1, AD-1423249.1, AD-1423250.1, AD-1423251.1, AD-1423252.1, AD-1423253.1, AD-1423254.1, AD-1423255.1, AD-1423256.1, AD-1423257.1, AD-1423258.1, AD-1423259.1, AD-1423260.1, AD-1423261.1, AD-1423262.1, AD-1423263.1, AD-1423264.1, AD-1423265.1, AD-1423266.1, AD-1423267.1, AD-

1423268.1, AD-1423269.1, AD-1423270.1, AD-1423271.1, AD-1423272.1, AD-1423273.1, AD-1423274.1, AD-1423275.1, AD-1423276.1, AD-1423277.1, AD-1423278.1, AD-1423279.1, AD-1423280.1, AD-1423281.1, AD-1423282.1, AD-1423283.1, AD-1423284.1, AD-1423285.1, AD-1423286.1, AD-1423287.1, AD-1423288.1, AD-1423289.1, AD-1423290.1, AD-1423291.1, AD-5 1423292.1, AD-1423293.1, AD-1423294.1, AD-1423295.1, AD-1423296.1, AD-1423297.1, AD-1423298.1, AD-1423299.1, AD-1423300.1, AD-1397266.1, AD-1397266.2, AD-1397267.1, AD-1423301.1, AD-1397268.1, AD-1397268.2, AD-1397269.1, AD-1423302.1, AD-1397270.1, AD-1397270.2, AD-1397271.1, AD-1397271.2, AD-1397272.1, AD-1423303.1, AD-1397273.1, AD-1423304.1, AD-1397274.1, AD-1423305.1, AD-1397275.1, AD-1423306.1, AD-1397276.1, AD-10 1397277.1, AD-1397277.2, AD-1397278.1, AD-1397279.1, AD-1397280.1, AD-1397281.1, AD-1397282.1, AD-1397283.1, AD-1397284.1, AD-1397285.1, AD-1397286.1, AD-1397287.1, AD-1397079.1, AD-1397079.2, AD-1397288.1, AD-1397289.1, AD-1397290.1, AD-1397080.1, AD-1397080.2, AD-1397291.1, AD-1397292.1, AD-1397293.1, AD-1397294.1, AD-1397081.1, AD-1397081.2, AD-1397295.1, AD-1397082.1, AD-1397082.2, AD-1397083.1, AD-1397083.2, AD-15 1397296.1, AD-1397297.1, AD-1397298.1, AD-1397299.1, AD-1397300.1, AD-1397301.1, AD-1397302.1, AD-1397084.1, AD-1397085.1, AD-1397086.1, AD-1397303.1, AD-1397087.1, AD-1397087.2, AD-1397304.1, AD-1397305.1, AD-1397306.1, AD-1397307.1, AD-1397308.1, AD-1397309.1, AD-1397310.1, AD-1397311.1, AD-1397312.1, AD-1397313.1, AD-1397314.1, AD-1397315.1, AD-1397316.1, AD-1397317.1, AD-1397318.1, AD-1397319.1, AD-1397320.1, AD-20 1397321.1, AD-1397322.1, AD-1397088.1, AD-1397089.1, AD-1397090.1, AD-1397091.1, AD-1397092.1, AD-1397093.1, AD-1397094.1, AD-1397095.1, AD-1397096.1, AD-1397097.1, AD-1397098.1, AD-1397099.1, AD-1397101.1, AD-1397102.1, AD-1397103.1, AD-1397104.1, AD-1397105.1, AD-1397106.1, AD-1397107.1, AD-1397108.1, AD-1397109.1, AD-1397110.1, AD-1397111.1, AD-1397112.1, AD-1397113.1, AD-1397114.1, AD-1397115.1, AD-1397116.1, AD-25 1397117.1, AD-1397118.1, AD-1397119.1, AD-1397120.1, AD-1397121.1, AD-1397122.1, AD-1397123.1, AD-1397124.1, AD-1397125.1, AD-1397126.1, AD-1397127.1, AD-1397128.1, AD-1397129.1, AD-1397130.1, AD-1397131.1, AD-1397132.1, AD-1397133.1, AD-1397134.1, AD-1397135.1, AD-1397136.1, AD-1397137.1, AD-1397138.1, AD-1397139.1, AD-1397140.1, AD-1397141.1, AD-1397142.1, AD-1397143.1, AD-1397144.1, AD-1397145.1, AD-1397146.1, AD-30 1397147.1, AD-1397148.1, AD-1397149.1, AD-1397150.1, AD-1397151.1, AD-1397152.1, AD-1397153.1, AD-1397154.1, AD-1397155.1, AD-1397156.1, AD-1397157.1, AD-1397158.1, AD-1397159.1, AD-1397160.1, AD-1397161.1, AD-1397162.1, AD-1397163.1, AD-1397164.1, AD-1397165.1, AD-1397166.1, AD-1397167.1, AD-1397168.1, AD-1397169.1, AD-1397170.1, AD-1397171.1, AD-1397172.1, AD-1397173.1, AD-1397174.1, AD-1397175.1, AD-1397176.1, AD-35 1397177.1, AD-1397178.1, AD-1397179.1, AD-1397180.1, AD-1397181.1, AD-1397182.1, AD-1397183.1, AD-1397184.1, AD-1397185.1, AD-1397186.1, AD-1397187.1, AD-1397188.1, AD-1397189.1, AD-1397190.1, AD-1397191.1, AD-1397192.1, AD-1397193.1, AD-1397194.1, AD-1397195.1, AD-1397196.1, AD-1397197.1, AD-1397198.1, AD-1397199.1, AD-1397200.1, AD-1397201.1, AD-1397202.1, AD-1397203.1, AD-1397204.1, AD-1397205.1, AD-1397206.1, AD-

1397207.1, AD-1397208.1, AD-1397209.1, AD-1397210.1, AD-1397211.1, AD-1397212.1, AD-1397213.1, AD-1397214.1, AD-1397215.1, AD-1397216.1, AD-1397217.1, AD-1397218.1, AD-1397219.1, AD-1397220.1, AD-1397221.1, AD-1397222.1, AD-1397223.1, AD-1397224.1, AD-1397225.1, AD-1397226.1, AD-1397227.1, AD-1397228.1, AD-1397229.1, AD-1397230.1, AD-1397231.1, AD-1397232.1, AD-1397233.1, AD-1397234.1, AD-1397235.1, AD-1397236.1, AD-1397237.1, AD-1397238.1, AD-1397239.1, AD-1397240.1, AD-1397241.1, AD-1397242.1, AD-1397243.1, AD-1397244.1, AD-1397245.1, AD-1397246.1, AD-1397247.1, AD-1397248.1, AD-1397249.1, AD-523565.1, AD-1397072.3, AD-1397073.3, AD-1397076.3, AD-1397077.3, AD-1397078.3, AD-1397252.2, AD-1397257.2, AD-1397258.2, AD-1397259.2, AD-1397263.2, AD-1397264.2, AD-1397309.2, AD-64958.114, AD-393758.4, AD-1397080.3, AD-1397293.2, AD-1397294.2, AD-1397081.3, AD-1397083.3, AD-1397298.2, AD-1397299.2, AD-1397084.2, AD-1397085.2, AD-1397087.3, AD-1397306.2, AD-1397307.2, AD-1397308.2, AD-1397088.2, AD-1566238, AD-1566239, AD-1566240, AD-1566241, AD-1566242, AD-1566243, AD-1566244, AD-1566245, AD-1566246, AD-1091965, AD-1566248, AD-1566249, AD-1566250, AD-1091966, AD-1566251, AD-1566252, AD-1566253, AD-1566254, AD-1566255, AD-1566256, AD-1566257, AD-1566258, AD-1566259, AD-692906, AD-1566575, AD-1566576, AD-1566577, AD-1566580, AD-1566581, AD-1566582, AD-1566583, AD-1566584, AD-1566586, AD-1566587, AD-1566588, AD-1566590, AD-1566591, AD-1566634, AD-1566635, AD-1566638, AD-1566639, AD-1566641, AD-1566642, AD-1566643, AD-1566679, AD-1566861, AD-1567153, AD-1567154, AD-1567157, AD-1567159, AD-1567160, AD-1567161, AD-1567164, AD-1567167, AD-1567199, AD-1567202, AD-1567550, AD-1567554, AD-1567784, AD-1567896, AD-1567897, AD-1568105, AD-1568108, AD-1568109, AD-1568139, AD-1568140, AD-1568143, AD-1568144, AD-1568148, AD-1568150, AD-1568151, AD-1568152, AD-1568153, AD-1568154, AD-1568158, AD-1568161, AD-1568172, AD-1568174, AD-1568175, AD-692908, AD-1568176, AD-1569830, AD-1569832, AD-1569834, AD-1569835, AD-1569862, AD-1569872, AD-1569890 and AD-1569892.

In a particular embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1 and AD-526993.1. In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1 and AD-523796.1.

In some embodiments, the present invention provides a dsRNA agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 12-13.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 1065-1085, 1195-1215, 1066-1086, 1068-1088, 705-725, 1067-1087, 4520-4540, 3341-3361, 4515-4535, 5284-5304, 5285-5305, 344-364, 5283-5303, 5354-5374, 2459-2479, 1061-1081, 706-726, 972-992, 4564-4584, 995-1015, 4546-4566, 968-988, 1127-1147, 4534-4554, 158-178, 4494-4514, 1691-1711, 3544-3564, 198-218, 979-999, 4548-4568, 4551-4571, 543-563, 715-735, 542-562, 352-372, 362-382, 4556-4576, 4547-4567, 4542-4562, 4558-4578, 4549-4569, 5074-5094, 4552-4572, 5073-5093, 5076-5096, 4550-4570 and 2753-2773 of SEQ ID NO: 5, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 6.

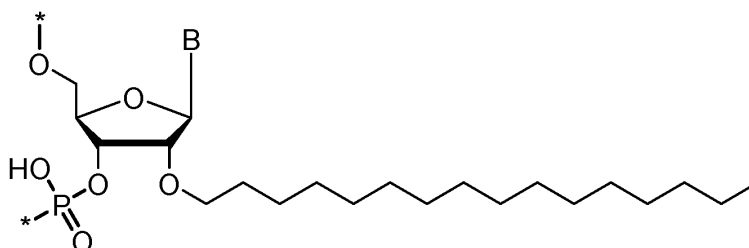
In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-393758.1, AD-393888.1, AD-393759.1, AD-393761.1, AD-393495.1, AD-393760.1, AD-396425.1, AD-395441.1, AD-396420.1, AD-397103.1, AD-397104.1, AD-393239.1, AD-397102.1, AD-397167.1, AD-394791.1, AD-393754.1, AD-393496.1, AD-393667.1, AD-396467.1, AD-393690.1, AD-396449.1, AD-393663.1, AD-393820.1, AD-396437.1, AD-393084.1, AD-396401.1, AD-394296.1, AD-395574.1, AD-393124.1, AD-393674.1, AD-396451.1, AD-396454.1, AD-393376.1, AD-393505.1, AD-393375.1, AD-393247.1, AD-393257.1, AD-396459.1, AD-396450.1, AD-396445.1, AD-396461.1, AD-396452.1, AD-396913.1, AD-396455.1, AD-396912.1, AD-396915.1, AD-396453.1 and AD-394991.1.

In one embodiment, the nucleotide sequence of the sense strand comprises at least 15 contiguous nucleotides corresponding to the MAPT gene exon 10 sense strand sequence set forth in SEQ ID NO.: 1533 and an antisense strand comprising a sequence complementary thereto.

In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences in Tables 6-8, 13, 17, 19, 21, 23, 26 and 28, are described as modified or conjugated sequences, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA of the disclosure, may comprise any one of the sequences set forth in any one of Tables 3-8, 12-13, and 16-28, that is un-modified, un-conjugated, or modified or conjugated differently than described therein. For example, although the sense strands of the agents of the invention may be conjugated to a GalNAc ligand, these agents may be conjugated to a moiety that directs delivery to the CNS, *e.g.*, a C16 ligand, as described herein. In one embodiment, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain (*e.g.*, a linear C16 alkyl or alkenyl). A lipophilic

ligand can be included in any of the positions provided in the instant application. In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage of the double-stranded iRNA agent. For example, a C16 ligand may be conjugated via the 2'-oxygen of a ribonucleotide as shown in the following structure:



where * denotes a bond to an adjacent nucleotide, and B is a nucleobase or a nucleobase analog, optionally where B is adenine, guanine, cytosine, thymine or uracil. Design and Synthesis of the ligands and monomers provided herein are described, for example, in PCT publication Nos. WO2019/217459, WO2020/132227, and WO2020/257194, contents of which are incorporated herein by reference in their entirety.

In some embodiments, the double-stranded iRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In one embodiment, the phosphate mimic is a 5'-vinyl phosphonate (VP). In some embodiments, the 5'-end of the antisense strand of the double-stranded iRNA agent does not contain a 5'-vinyl phosphonate (VP).

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.*, 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of a MAPT gene by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% inhibition relative to a control level, from a dsRNA comprising the full sequence using the *in vitro* assay with, *e.g.*, A549 cells and a 10 nM concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure. In some embodiments, inhibition from a dsRNA comprising the full sequence was measured using the *in vitro* assay with primary mouse hepatocytes.

In addition, the RNAs described herein identify a site(s) in a MAPT transcript that is susceptible to RISC-mediated cleavage. As such, the present disclosure further features RNAi agents that target within this site(s). As used herein, an RNAi agent is said to target within a particular site of an RNA transcript if the RNAi agent promotes cleavage of the transcript anywhere within that particular site. Such an RNAi agent will generally include at least about 15 contiguous nucleotides, preferably at least 19 nucleotides, from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a MAPT gene.

III. Modified RNAi Agents of the Disclosure

In one embodiment, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA, is unmodified, and does not comprise, *e.g.*, chemical modifications or conjugations known in the art and described herein. In preferred embodiments, the RNA of an RNAi agent of the disclosure, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the disclosure, substantially all of the nucleotides of an RNAi agent of the disclosure are modified. In other embodiments of the disclosure, all of the nucleotides of an RNAi agent of the disclosure are modified. RNAi agents of the disclosure in which “substantially all of the nucleotides are modified” are largely but not wholly modified and can include not more than 5, 4, 3, 2, or unmodified nucleotides. In still other embodiments of the disclosure, RNAi agents of the disclosure can include not more than 5, 4, 3, 2 or 1 modified nucleotides.

The nucleic acids featured in the disclosure can be synthesized or modified by methods well established in the art, such as those described in “Current protocols in nucleic acid chemistry,” Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNAi agents useful in the embodiments described herein include, but are not limited to, RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified RNAi agent will have a phosphorus atom in its internucleoside backbone.

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

thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. In some embodiments of the invention, the dsRNA agents of the invention are in a free acid form. In other embodiments of the invention, the dsRNA agents of the invention are in a salt form. In one embodiment, the dsRNA agents of the invention are in a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothioate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothioate groups present in the agent.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

In other embodiments, suitable RNA mimetics are contemplated for use in RNAi agents, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are

replaced with alternate groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, a RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the RNAi agents of the disclosure are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

Some embodiments featured in the disclosure include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH₂--NH--CH₂--, --CH₂--N(CH₃)--O--CH₂--[known as a methylene (methylimino) or MMI backbone], --CH₂--O--N(CH₃)--CH₂--, --CH₂--N(CH₃)--N(CH₃)--CH₂-- and --N(CH₃)--CH₂---[wherein the native phosphodiester backbone is represented as --O--P--O--CH₂--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced US5,034,506.

Modified RNAs can also contain one or more substituted sugar moieties. The RNAi agents, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an RNAi agent, or a group for improving the pharmacodynamic properties of an RNAi agent, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethyl (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH₂--O--CH₂--N(CH₂)₂. Further exemplary modifications include: 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂), 2'-O-hexadecyl, and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an RNAi agent, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. RNAi agents can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application. The entire contents of each of the foregoing are hereby incorporated herein by reference.

An RNAi agent of the disclosure can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L., ed. John Wiley & Sons, 1990, those disclosed by Englisch *et al.*, (1991) *Angewandte Chemie, International Edition*, 30:613, and those disclosed by Sanghvi, Y. S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., *dsRNA Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272;

5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

5 An RNAi agent of the disclosure can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

10 An RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring. Thus, in some embodiments an agent of the disclosure may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the disclosure include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the disclosure include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to 4'-(CH₂)—O-2' (LNA); 4'-(CH₂)—S-2'; 4'-(CH₂)₂—O-2' (ENA); 4'-CH(CH₃)—O-2' (also referred to as "constrained ethyl" or "cEt") and 4'-CH(CH₂OCH₃)—O-2' (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4'-C(CH₃)(CH₃)—O-2' (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4'-CH₂—N(OCH₃)-2' (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4'-CH₂—O—N(CH₃)-2' (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4'-CH₂—N(R)—O-2', wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4'-CH₂—C(H)(CH₃)-2' (see, *e.g.*, Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4'-CH₂—C(=CH₂)-2' (and analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative US Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: US Patent Nos.

6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

5 Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α -L-ribofuranose and β -D-ribofuranose (see WO 99/14226).

10 An RNAi agent of the disclosure can also be modified to include one or more constrained ethyl nucleotides. As used herein, a “constrained ethyl nucleotide” or “cEt” is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as “S-cEt.”

15 An RNAi agent of the disclosure may also include one or more “conformationally restricted nucleotides” (“CRN”). CRN are nucleotide analogs with a linker connecting the C2' and C4' carbons of ribose or the C3 and -C5' carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US 2013/0190383; and WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

20 In some embodiments, an RNAi agent of the disclosure comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked “sugar” residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series*, 52, 133-134 (2008) and Fluiter et al., *Mol. Biosyst.*, 2009, 10, 1039 hereby incorporated by reference).

30 Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

35 An RNAi agent of the disclosure may also include one or more “cyclohexene nucleic acids” or (“CeNA”). CeNA are nucleotide analogs with a replacement of the furanose moiety of DNA by a cyclohexene ring. Incorporation of cyclohexenyl nucleosides in a DNA chain increases the stability of a DNA/RNA hybrid. CeNA is stable against degradation in serum and a CeNA/RNA hybrid is able to activate *E. Coli* RNase H, resulting in cleavage of the RNA strand. (see Wang et al., *Am. Chem. Soc.* 2000, 122, 36, 8595–8602, hereby incorporated by reference).

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-

(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO 2011/005861.

Other modifications of an RNAi agent of the disclosure include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic on the antisense strand of an RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified Rnai Agents Comprising Motifs Of The Disclosure

In certain aspects of the disclosure, the double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in WO 2013/075035, the entire contents of which are incorporated herein by reference. As shown herein and in WO 2013/075035, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The RNAi agent may be optionally conjugated with a lipophilic ligand, *e.g.*, a C16 ligand, for instance on the sense strand. The RNAi agent may be optionally modified with a (S)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand. The resulting RNAi agents present superior gene silencing activity.

Accordingly, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, a MAPT gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be 15-30 nucleotides in length. For example, each strand may be 16-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length. In certain embodiments, each strand is 19-23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 15-30 nucleotide pairs in length. For example, the duplex region can be 16-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length. In preferred embodiments, the duplex region is 19-21 nucleotide pairs in length.

In one embodiment, the RNAi agent may contain one or more overhang regions or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length,

1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. In preferred embodiments, the nucleotide overhang region is 2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but not limited to 2'-sugar modified, such as, 2-F, 2'-O-methyl, thymidine (T), and any combinations thereof.

For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In one embodiment, the RNAi agent is double blunt-ended and 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In another embodiment, the RNAi agent is double blunt-ended and 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, 10 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In yet another embodiment, the RNAi agent is a double blunt-ended and 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three

consecutive nucleotides at positions 9, 10, 11 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end.

In one embodiment, the RNAi agent comprises a 21 nucleotide sense strand and a 23
 5 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5' end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. Preferably, the 2 nucleotide overhang is at the 3'-end of the
 10 antisense strand. When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the
 15 sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.*, in an alternating motif. Optionally, the RNAi agent further comprises a ligand (*e.g.*, a lipophilic ligand, optionally a C16 ligand).

In one embodiment, the RNAi agent comprises a sense and an antisense strand, wherein the
 20 sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex;
 25 wherein at least the 3' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides
 30 are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one
 35 motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides

and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

In one embodiment, the antisense strand of the RNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand.

For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the RNAi from the 5'-end.

The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adjacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other, then the chemistry of the motifs are distinct from each other and when the

motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

5 Like the sense strand, the antisense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

10 In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

 In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region
15 at the 3'-end, 5'-end or both ends of the strand.

 When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

 When the sense strand and the antisense strand of the RNAi agent each contain at least two
20 wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two, or three nucleotides in the duplex region.

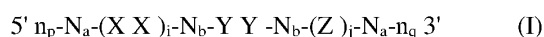
25 In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis
30 can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

 In one embodiment, the RNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base
35 pairs within the duplex regions from the 5'- end of the antisense strand independently selected from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In one embodiment, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):



wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

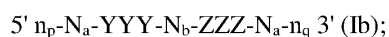
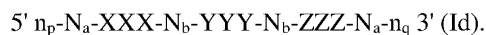
wherein N_b and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. Preferably YYY is all 2'-F modified nucleotides.

In one embodiment, the N_a or N_b comprise modifications of alternating pattern.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8, 7, 8, 9, 8, 9, 10, 9, 10, 11, 10, 11,12 or 11, 12, 13) of the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end.

In one embodiment, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:



When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides.

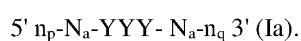
Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

5 When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

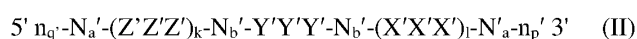
Each of X, Y and Z may be the same or different from each other.

10 In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:



When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

15 In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):



wherein:

k and l are each independently 0 or 1;

20 p' and q' are each independently 0-6;

each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p' and n_q' independently represent an overhang nucleotide;

25 wherein N_b' and Y' do not have the same modification;

and $X'X'X'$, $Y'Y'Y'$ and $Z'Z'Z'$ each independently represent one motif of three identical modifications on three consecutive nucleotides.

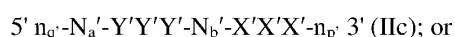
In one embodiment, the N_a' or N_b' comprise modifications of alternating pattern.

30 The $Y'Y'Y'$ motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotide in length, the $Y'Y'Y'$ motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end. Preferably, the $Y'Y'Y'$ motif occurs at positions 11, 12, 13.

35 In one embodiment, $Y'Y'Y'$ motif is all 2'-OMe modified nucleotides.

In one embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

The antisense strand can therefore be represented by the following formulas:



5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_b'-X'X'X'-N_a'-n_p' 3' (IIId).

When the antisense strand is represented by formula (IIb), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IIc), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IIId), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

5' n_p'-N_a'-Y'Y'Y'-N_a'-n_q' 3' (Ia).

When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X', Y' and Z' may be the same or different from each other.

Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y' and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

In one embodiment, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

In one embodiment the antisense strand may contain Y'Y'Y' motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end; and Y' represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with an antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, the RNAi agents for use in the methods of the disclosure may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (III):

sense: $5' n_p - N_a - (X X X)_i - N_b - Y Y Y - N_b - (Z Z Z)_j - N_a - n_q 3'$

antisense: $3' n_p' - N_a' - (X'X'X')_k - N_b' - Y'Y'Y' - N_b' - (Z'Z'Z')_l - N_a' - n_q' 5'$ (III)

wherein:

10 i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

15 each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein

each n_p , n_p , n_q , and n_q , each of which may or may not be present, independently represents an overhang nucleotide; and

20 XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

Exemplary combinations of the sense strand and antisense strand forming an RNAi duplex include the formulas below:

$5' n_p - N_a - Y Y Y - N_a - n_q 3'$

$3' n_p' - N_a' - Y'Y'Y' - N_a' - n_q' 5'$ (IIIa)

$5' n_p - N_a - Y Y Y - N_b - Z Z Z - N_a - n_q 3'$

$3' n_p' - N_a' - Y'Y'Y' - N_b' - Z'Z'Z' - N_a' - n_q' 5'$ (IIIb)

30 $5' n_p - N_a - X X X - N_b - Y Y Y - N_a - n_q 3'$

$3' n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_a' - n_q' 5'$ (IIIc)

$5' n_p - N_a - X X X - N_b - Y Y Y - N_b - Z Z Z - N_a - n_q 3'$

$3' n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_b' - Z'Z'Z' - N_a' - n_q' 5'$ (IIId)

When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIIc), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

5 When the RNAi agent is represented as formula (IIId), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a , N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a , N_a' , N_b and N_b' independently comprises modifications of alternating pattern.

10 In one embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications
15 are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage, and the sense strand is conjugated to one or more C16 (or related) moieties attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide *via*
20 phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties, optionally attached through a bivalent or trivalent branched linker.

In one embodiment, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a
25 neighboring nucleotide *via* phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties attached through a bivalent or trivalent branched linker.

In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a
30 linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

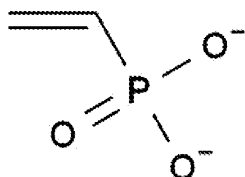
In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are
35 connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally

conjugated to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the entire contents of each of which are hereby incorporated herein by reference.

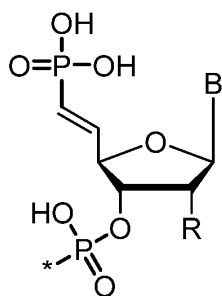
In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a vinyl phosphonate of the disclosure has the following structure:



10

A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA. The dsRNA agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl. When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-E-VP isomer (i.e., trans-vinylphosphate, isomer (i.e., cis-vinylphosphate,) or mixtures thereof.

For example, when the phosphate mimic is a 5'-vinyl phosphonate (VP), the 5'-terminal nucleotide can have the following structure,

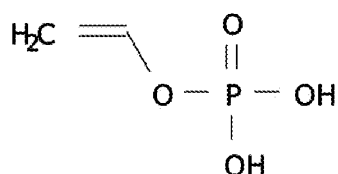


wherein * indicates the location of the bond to 5'-position of the adjacent nucleotide;

R is hydrogen, hydroxy, methoxy or fluoro (e.g., hydroxy); and

B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine or uracil.

Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure is:

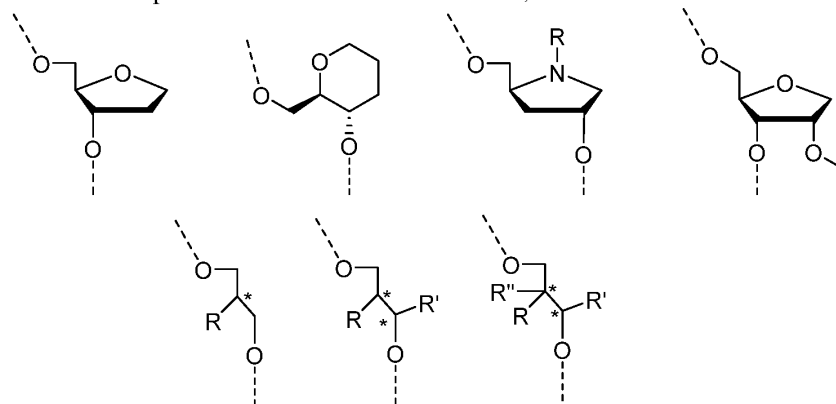


i. Thermally Destabilizing Modifications

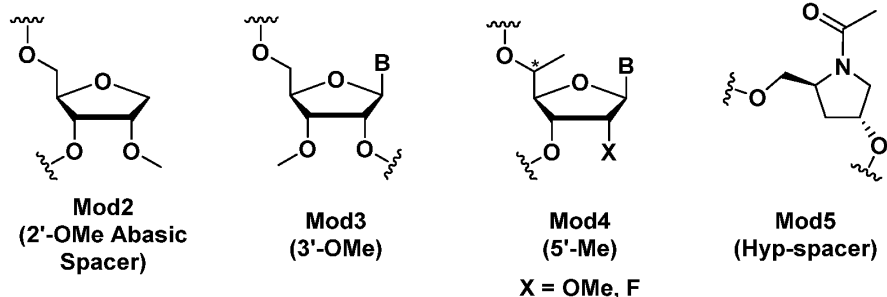
In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing. It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, or preferably positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7 or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (T_m) (preferably a T_m with one, two, three or four degrees lower than the T_m of the dsRNA without having such modification(s)). In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5 or 9 from the 5'-end of the antisense strand.

The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification or acyclic nucleotide, *e.g.*, unlocked nucleic acids (UNA) or glycol nucleic acid (GNA).

Exemplified abasic modifications include, but are not limited to the following:

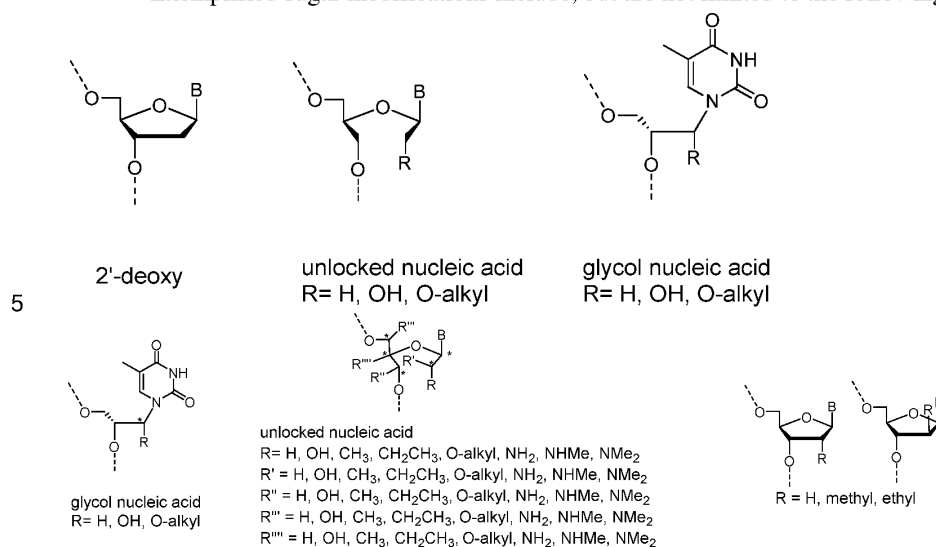


Wherein R = H, Me, Et or OMe; R' = H, Me, Et or OMe; R'' = H, Me, Et or OMe



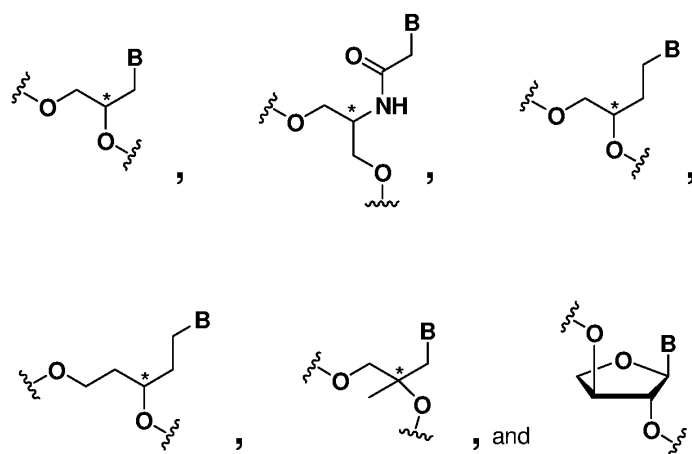
wherein B is a modified or unmodified nucleobase.

Exemplified sugar modifications include, but are not limited to the following:



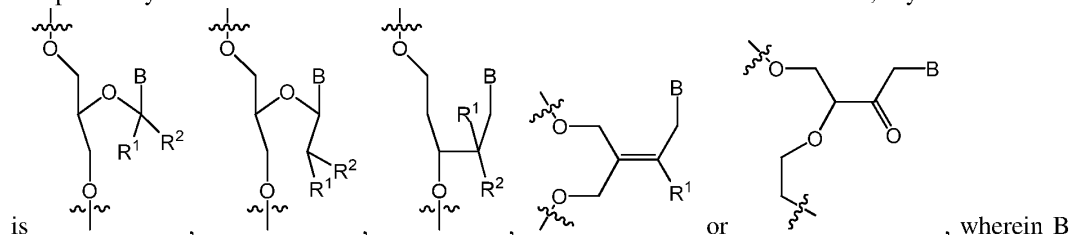
wherein B is a modified or unmodified nucleobase.

In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:



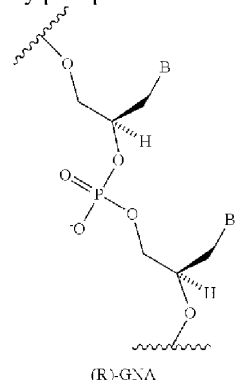
wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

The term “acyclic nucleotide” refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4' or O4') are independently or in combination absent from the nucleotide. In some embodiments, acyclic nucleotide



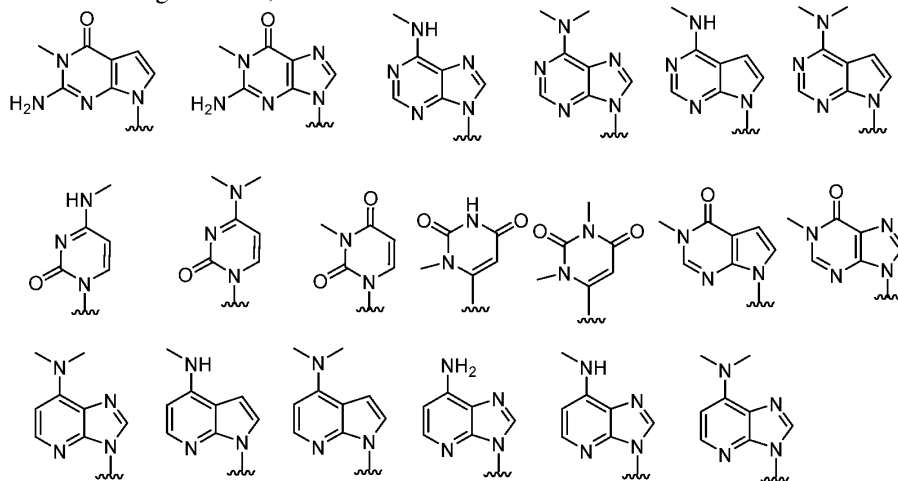
is a modified or unmodified nucleobase, R¹ and R² independently are H, halogen, OR₃, or alkyl; and R₃ is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic nucleotide can be linked *via* 2'-5' or 3'-5' linkage.

The term ‘GNA’ refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its “backbone” in that is composed of repeating glycerol units linked by phosphodiester bonds:



The thermally destabilizing modification of the duplex can be mismatches (*i.e.*, noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, U:T, or a combination thereof. Other mismatch base pairings known in the art are also amenable to the present invention. A mismatch can occur between nucleotides that are either naturally occurring nucleotides or modified nucleotides, *i.e.*, the mismatch base pairing can occur between the nucleobases from respective nucleotides independent of the modifications on the ribose sugars of the nucleotides. In certain embodiments, the dsRNA molecule contains at least one nucleobase in the mismatch pairing that is a 2'-deoxy nucleobase; *e.g.*, the 2'-deoxy nucleobase is in the sense strand.

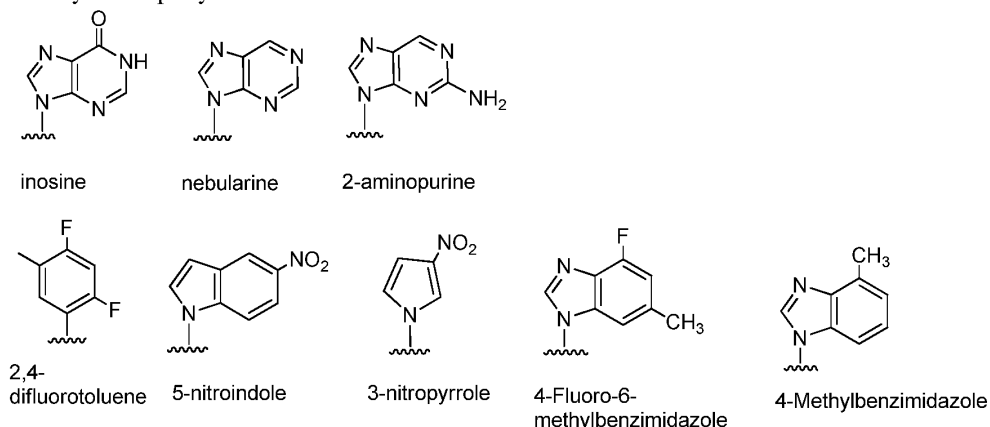
In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:



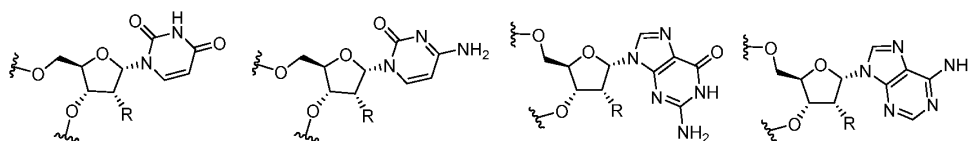
- 5 More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

The thermally destabilizing modifications may also include universal base with reduced or abolished capability to form hydrogen bonds with the opposing bases, and phosphate modifications.

- 10 In some embodiments, the thermally destabilizing modification of the duplex includes nucleotides with non-canonical bases such as, but not limited to, nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand. These nucleobase modifications have been evaluated for destabilization of the central region of the dsRNA duplex as described in WO 2010/0011895, which is herein incorporated by reference in its
- 15 entirety. Exemplary nucleobase modifications are:

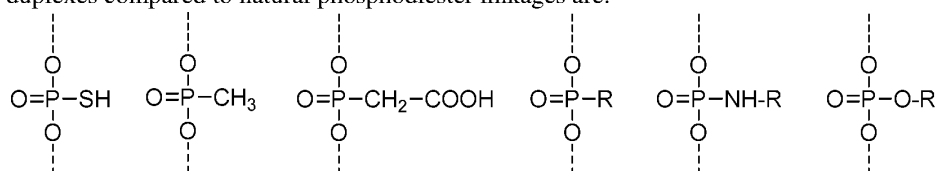


In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes one or more α -nucleotide complementary to the base on the target mRNA, such as:



wherein R is H, OH, OCH₃, F, NH₂, NHMe, NMe₂ or O-alkyl.

Exemplary phosphate modifications known to decrease the thermal stability of dsRNA duplexes compared to natural phosphodiester linkages are:



5 R = alkyl

The alkyl for the R group can be a C₁-C₆alkyl. Specific alkyls for the R group include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

As the skilled artisan will recognize, in view of the functional role of nucleobases is defining specificity of an RNAi agent of the disclosure, while nucleobase modifications can be performed in the various manners as described herein, *e.g.*, to introduce destabilizing modifications into an RNAi agent of the disclosure, *e.g.*, for purpose of enhancing on-target effect relative to off-target effect, the range of modifications available and, in general, present upon RNAi agents of the disclosure tends to be much greater for non-nucleobase modifications, *e.g.*, modifications to sugar groups or phosphate backbones of polyribonucleotides. Such modifications are described in greater detail in other sections of the instant disclosure and are expressly contemplated for RNAi agents of the disclosure, either possessing native nucleobases or modified nucleobases as described above or elsewhere herein.

In addition to the antisense strand comprising a thermally destabilizing modification, the dsRNA can also comprise one or more stabilizing modifications. For example, the dsRNA can comprise at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, the stabilizing modifications all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two stabilizing modifications. The stabilizing modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the stabilizing modification can occur on every nucleotide on the sense strand or antisense strand; each stabilizing modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both stabilizing modification in an alternating pattern. The alternating pattern of the stabilizing modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the stabilizing modifications on the sense strand can have a shift relative to the alternating pattern of the stabilizing modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the antisense strand can be present at any positions. In some embodiments, the

antisense comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises stabilizing modifications at positions 2, 14, and 16 from the 5'-end.

5 In some embodiments, the antisense strand comprises at least one stabilizing modification adjacent to the destabilizing modification. For example, the stabilizing modification can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a stabilizing modification at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*,
10 positions -1 and +1 from the position of the destabilizing modification.

 In some embodiments, the antisense strand comprises at least two stabilizing modifications at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

 In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six,
15 seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the sense strand can be present at any positions. In some embodiments, the sense strand comprises stabilizing modifications at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises stabilizing modifications at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises stabilizing modifications at positions
20 opposite or complementary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises stabilizing modifications at positions opposite or complementary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four stabilizing modifications.

25 In some embodiments, the sense strand does not comprise a stabilizing modification in position opposite or complementary to the thermally destabilizing modification of the duplex in the antisense strand.

 Exemplary thermally stabilizing modifications include, but are not limited to, 2'-fluoro modifications. Other thermally stabilizing modifications include, but are not limited to, LNA.

30 In some embodiments, the dsRNA of the disclosure comprises at least four (*e.g.*, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, the 2'-fluoro nucleotides all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two 2'-fluoro nucleotides. The 2'-fluoro modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the 2'-fluoro modification can occur
35 on every nucleotide on the sense strand or antisense strand; each 2'-fluoro modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both 2'-fluoro modifications in an alternating pattern. The alternating pattern of the 2'-fluoro modifications on the sense strand may be the same or different from the antisense strand, and

the alternating pattern of the 2'-fluoro modifications on the sense strand can have a shift relative to the alternating pattern of the 2'-fluoro modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one 2'-fluoro nucleotide adjacent to the destabilizing modification. For example, the 2'-fluoro nucleotide can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two 2'-fluoro nucleotides at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the sense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complementary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complementary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three or four 2'-fluoro nucleotides.

In some embodiments, the sense strand does not comprise a 2'-fluoro nucleotide in position opposite or complementary to the thermally destabilizing modification of the duplex in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide occurs in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), wherein one end of the dsRNA is blunt, while the other end is comprises a 2 nt overhang, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the

antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a blunt end at 5'-end of the antisense strand. Preferably, the 2 nt overhang is at the 3'-end of the antisense.

In some embodiments, the dsRNA molecule of the disclosure comprising a sense and antisense strands, wherein: the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1), positions 1 to 23 of said sense strand comprise at least 8 ribonucleotides; antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when said double stranded nucleic acid is introduced into a mammalian cell; and wherein the antisense strand contains at least one thermally destabilizing nucleotide, where at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand). For example, the thermally destabilizing nucleotide occurs between positions opposite or complementary to positions 14-17 of the 5'-end of the sense strand, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a duplex region of 12-30 nucleotide pairs in length.

In some embodiments, the dsRNA molecule of the disclosure comprises a sense and antisense strands, wherein said dsRNA molecule comprises a sense strand having a length which is at least 25 and at most 29 nucleotides and an antisense strand having a length which is at most 30 nucleotides with the sense strand comprises a modified nucleotide that is susceptible to enzymatic degradation at position 11 from the 5' end, wherein the 3' end of said sense strand and the 5' end of said antisense strand form a blunt end and said antisense strand is 1-4 nucleotides longer at its 3' end than the sense strand, wherein the duplex region which is at least 25 nucleotides in length, and said antisense strand is sufficiently complementary to a target mRNA along at least 19 nt of said antisense strand length to

reduce target gene expression when said dsRNA molecule is introduced into a mammalian cell, and wherein dicer cleavage of said dsRNA preferentially results in an siRNA comprising said 3' end of said antisense strand, thereby reducing expression of the target gene in the mammal, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA has a duplex region of 12-29 nucleotide pairs in length.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNA molecule may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2' hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a single strand region of an RNA. *E.g.*, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. *E.g.*, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of

the nucleobase, and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In some embodiments, each residue of the sense strand and antisense strand is independently modified with locked nucleic acid (LNA), unlocked nucleic acid (UNA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-deoxy, or 2'-fluoro. The strands can contain more than one modification. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. It is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-deoxy, 2'-O-methyl or 2'-fluoro modifications, acyclic nucleotides or others. In some embodiments, the sense strand and antisense strand each comprises two differently modified nucleotides selected from 2'-O-methyl or 2'-deoxy. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl nucleotide, 2'-deoxy nucleotide, 2'-deoxy-2'-fluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, or 2'-ara-F nucleotide. Again, it is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises modifications of an alternating pattern, particular in the B1, B2, B3, B1', B2', B3', B4' regions. The term "alternating motif" or "alternative pattern" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB...", "AABBAABBAABB...", "AABAABAABAAB...", "AAABAABAABAAB...", "AAABBBAAABBB...", or "ABCABCABCABC...", etc.

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB...", "ACACAC..." "BDBDBD..." or "CDCDCD...", etc.

In some embodiments, the dsRNA molecule of the disclosure comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and vice versa. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 3'-5' of

the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 3'-5' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

The dsRNA molecule of the disclosure may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

In some embodiments, the dsRNA molecule comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region comprises two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. Preferably, these terminal three nucleotides may be at the 3'-end of the antisense strand.

In some embodiments, the sense strand of the dsRNA molecule comprises 1-10 blocks of two to ten phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said sense strand is paired with an antisense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the

oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of
5 three phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an
10 antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of four phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence
15 and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of five phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8,
20 9, 10, 11, or 12 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of six phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of
25 phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of seven phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, or 8 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate
35 internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of eight phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, or 6 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said
5 antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of nine phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, or 4
10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

15 In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s) of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage at one end or both ends of the sense or antisense strand.

20 In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the internal region of the duplex of each of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate methylphosphonate internucleotide linkage at position 8-16 of the duplex region counting from the 5'-end of the sense
25 strand; the dsRNA molecule can optionally further comprise one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s).

In some embodiments, the dsRNA molecule of the disclosure further comprises one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 1-5 and one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within
30 position 18-23 of the sense strand (counting from the 5'-end), and one to five phosphorothioate or methylphosphonate internucleotide linkage modifications at positions 1 and 2 and one to five within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate
35 or methylphosphonate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 2 and two phosphorothioate or methylphosphonate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 (counting from the 5'-end) of the sense strand, and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 (counting from the 5'-end) of the sense strand, and one phosphorothioate internucleotide linkage modification at position 1 or 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within positions 1-5 and one within positions 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within positions 1-5 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within positions 1-5 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at positions 20 and 21 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 and one at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 20 and 21 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 21 and 22 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two

phosphorothioate internucleotide linkage modifications at positions 21 and 22 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at positions 1 and 2, and two
5 phosphorothioate internucleotide linkage modifications at position 22 and 23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one
10 phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 22 and 23 the antisense strand (counting from the 5'-end).

15 In some embodiments, compound of the disclosure comprises a pattern of backbone chiral centers. In some embodiments, a common pattern of backbone chiral centers comprises at least 5 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 6 internucleotidic linkages in the Sp configuration. In some
20 embodiments, a common pattern of backbone chiral centers comprises at least 7 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 8 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 9 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration. In some
25 embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration. In some
30 embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 16 internucleotidic linkages in the Sp configuration. In some
35 embodiments, a common pattern of backbone chiral centers comprises at least 17 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 18 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 19 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of

backbone chiral centers comprises no more than 7 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages which are not chiral (as a non-limiting example, a phosphodiester). In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration, and no more than 8 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration, and no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration, and no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration, and no more than 4 internucleotidic linkages which are not chiral. In some embodiments, the internucleotidic linkages in the Sp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages in the Rp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages which are not chiral are optionally contiguous or not contiguous.

In some embodiments, compound of the disclosure comprises a block is a stereochemistry block. In some embodiments, a block is an Rp block in that each internucleotidic linkage of the block is Rp. In some embodiments, a 5'-block is an Rp block. In some embodiments, a 3'-block is an Rp block. In some embodiments, a block is an Sp block in that each internucleotidic linkage of the block is Sp. In some embodiments, a 5'-block is an Sp block. In some embodiments, a 3'-block is an Sp block. In some embodiments, provided oligonucleotides comprise both Rp and Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Rp but no Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Sp but no Rp blocks. In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

In some embodiments, compound of the disclosure comprises a 5'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units. In some embodiments, a 5'-block comprises 5 or more nucleoside units. In some embodiments, a 5'-block comprises 6 or more nucleoside units. In some embodiments, a 5'-block comprises 7 or more nucleoside units. In some embodiments, a 3'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block comprises 4 or more nucleoside units. In some embodiments, a 3'-block comprises 5 or more nucleoside units. In some embodiments, a 3'-block comprises 6 or more nucleoside units. In some embodiments, a 3'-block comprises 7 or more nucleoside units.

In some embodiments, compound of the disclosure comprises a type of nucleoside in a region or an oligonucleotide is followed by a specific type of internucleotidic linkage, *e.g.*, natural phosphate linkage, modified internucleotidic linkage, Rp chiral internucleotidic linkage, Sp chiral internucleotidic linkage, etc. In some embodiments, A is followed by Sp. In some embodiments, A is followed by Rp. In some embodiments, A is followed by natural phosphate linkage (PO). In some embodiments, U is followed by Sp. In some embodiments, U is followed by Rp. In some embodiments, U is followed by natural phosphate linkage (PO). In some embodiments, C is followed by Sp. In some embodiments, C is followed by Rp. In some embodiments, C is followed by natural phosphate linkage (PO). In some embodiments, G is followed by Sp. In some embodiments, G is followed by Rp. In some embodiments, G is followed by natural phosphate linkage (PO). In some embodiments, C and U are followed by Sp. In some embodiments, C and U are followed by Rp. In some embodiments, C and U are followed by natural phosphate linkage (PO). In some embodiments, A and G are followed by Sp. In some embodiments, A and G are followed by Rp.

In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide

positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (vii) the dsRNA has a blunt end at 5'-end of the antisense strand.

10 In some embodiments, the dsRNA molecule of the disclosure comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

15 In some embodiments, the dsRNA molecule of the disclosure comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand can be chosen independently from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

20 In some embodiments, the nucleotide at the 1 position within the duplex region from the 5'- end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

25 It was found that introducing 4'-modified or 5'-modified nucleotide to the 3'-end of a phosphodiester (PO), phosphorothioate (PS), or phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide can exert steric effect to the internucleotide linkage and, hence, protecting or stabilizing it against nucleases. In some embodiments, the introduction of a 4'-modified or a 5'-modified nucleotide to the 3'-end of a PO, PS, or PS2 linkage of a dinucleotide modifies the second nucleotide in the dinucleotide pair. In other 30 embodiments, the introduction of a 4'-modified or a 5'-modified nucleotide to the 3'-end of a PO, PS, or PS2 linkage of a dinucleotide modifies the nucleotide at the 3'-end of the dinucleotide pair.

35 In some embodiments, 5'-modified nucleotide is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 5'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded

siRNA. The alkyl group at the 5' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleotide is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

5 In some embodiments, 4'-modified nucleotide is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 4'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 4' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleotide is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer. Alternatively, a 4'-*O*-alkylated nucleoside may be introduced
10 at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The 4'-*O*-alkyl of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleotide is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

15 In some embodiments, 5'-alkylated nucleotide is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleotide is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

20 In some embodiments, 4'-alkylated nucleotide is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 4'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleotide is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

25 In some embodiments, 4'-*O*-alkylated nucleotide is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleotide is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

30 In some embodiments, the dsRNA molecule of the disclosure can comprise 2'-5' linkages (with 2'-H, 2'-OH and 2'-OMe and with P=O or P=S). For example, the 2'-5' linkages modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

35 In another embodiment, the dsRNA molecule of the disclosure can comprise L sugars (*e.g.*, L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugars modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

Various publications describe multimeric siRNA which can all be used with the dsRNA of the disclosure. Such publications include WO2007/091269, US 7858769, WO2010/141511,

WO2007/117686, WO2009/014887, and WO2011/031520 which are hereby incorporated by their entirety.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to an RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.*, a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide *via* a carrier. The carriers include (i) at least one “backbone attachment point,” preferably two “backbone attachment points” and (ii) at least one “tethering attachment point.” A “backbone attachment point” as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A “tethering attachment point” (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

In certain specific embodiments, the RNAi agent for use in the methods of the disclosure is an agent selected from the group of agents listed in any one of Tables 2-5, 9 or 10. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the invention involves chemically linking to the iRNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or

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

15 In certain embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some 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. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

20 Ligands can include a naturally occurring substance, such as a protein (*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); 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
 25 L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl) methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly (2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine,
 30 peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an α helical peptide.

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,
 35 Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, 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. In certain embodiments, the ligand is a multivalent galactose, *e.g.*, an N-acetyl-galactosamine.

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

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- κ B.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc.* Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc.* Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated iRNAs of the invention may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be

reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems® (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present invention are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. Lipid Conjugates

In certain embodiments, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as 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, naproxen 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, 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 (*e.g.*, inhibit) 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 certain embodiments, the lipid-based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

In certain embodiments, the lipid-based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid-based ligand.

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 are particularly 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).

10 *B. Cell Permeation Agents*

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 antennopodia. 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 is typically an α -helical agent and can have a lipophilic and a lipophobic phase.

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 iRNA agents can affect pharmacokinetic distribution of the iRNA, 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. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 1534). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 1535)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a “delivery” peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 1536)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 1537)) have been found to be capable of functioning as delivery peptides. 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). Typically, the peptide or peptidomimetic tethered to a dsRNA 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.

5 An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. Preferred conjugates of this ligand target PECAM-1 or VEGF.

10 An RGD peptide moiety can be used to target a particular cell type, *e.g.*, a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, *Cancer Res.*, 62:5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, *Cancer Gene Therapy* 8:783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.*, glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver an iRNA agent to a tumor cell expressing $\alpha_v\beta_3$ (Haubner *et al.*, *Jour. Nucl. Med.*, 42:326-336, 2001).

15 A "cell permeation peptide" is capable of permeating a cell, *e.g.*, a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α -helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β -defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, *Nucl. Acids Res.* 31:2717-2724, 2003).

C. Carbohydrate Conjugates

25 In some embodiments of the compositions and methods of the invention, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, 30 branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), 35 and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and tri-saccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, a carbohydrate conjugate comprises a monosaccharide.

In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular
5 cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached *via* a linker, *e.g.*, a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense
10 strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 3' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein. In some embodiments the GalNAc conjugate is conjugated to the 5' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 5' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein.

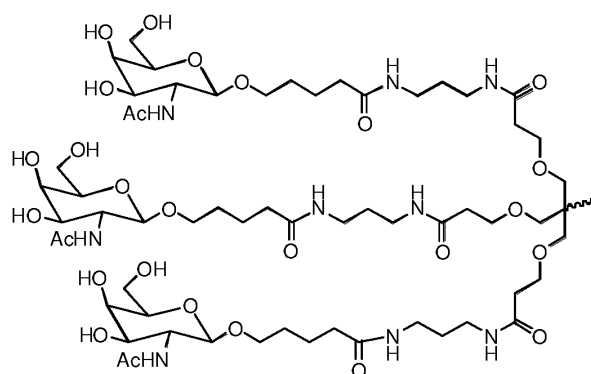
In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other
15 embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a tetravalent linker.
20

In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi
25 agent through a plurality of monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently
30 comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

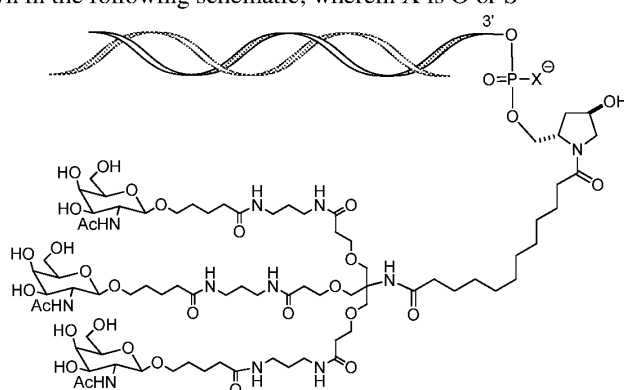
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a
35 plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

In some embodiments, the GalNAc conjugate is

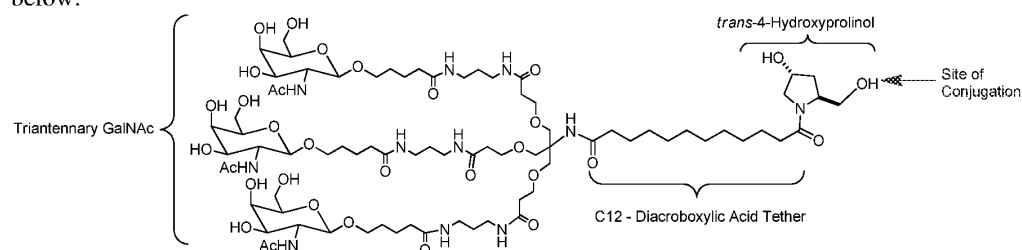


Formula II.

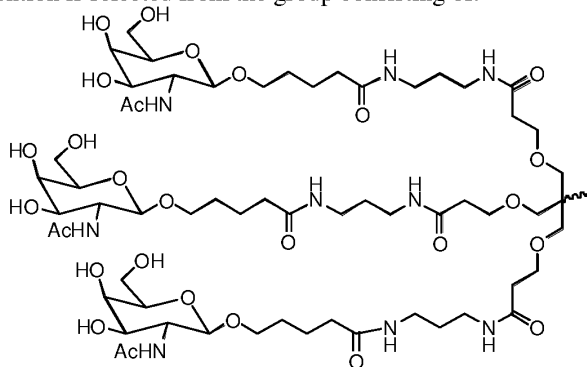
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



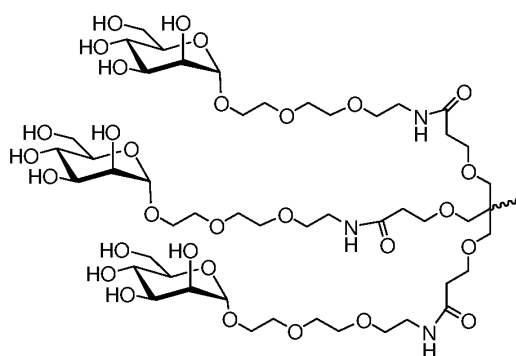
- 5 In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



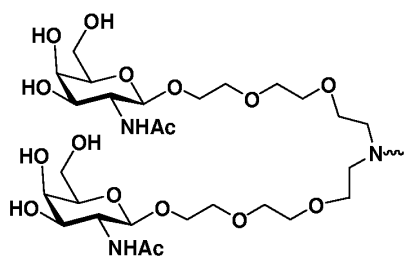
In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



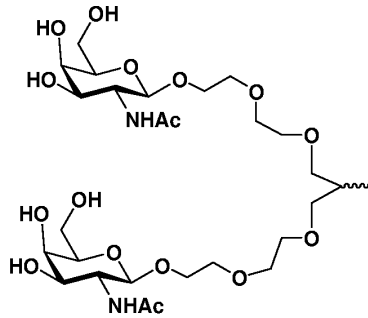
Formula II,



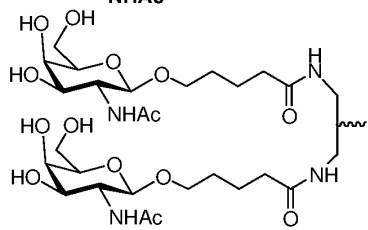
Formula III,



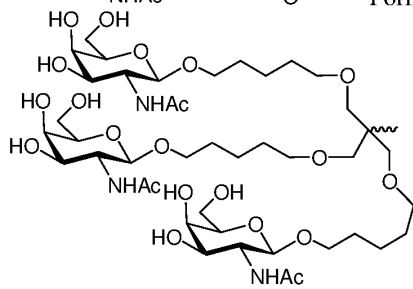
Formula IV,



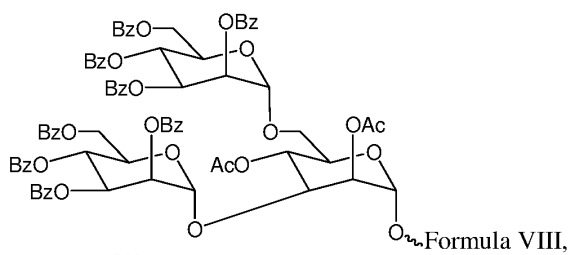
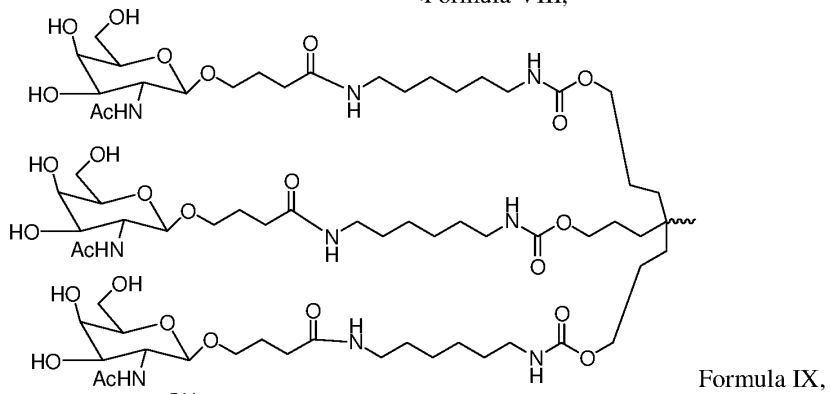
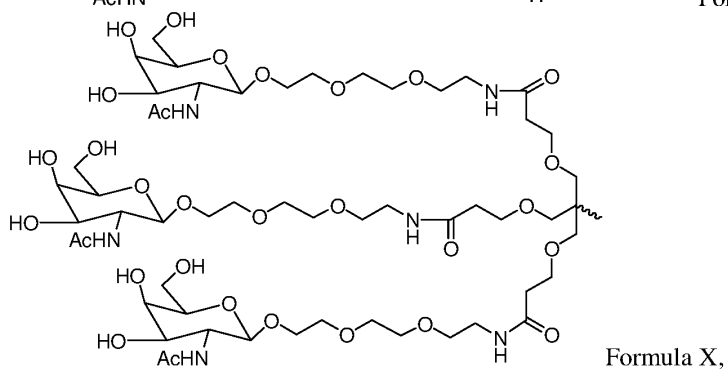
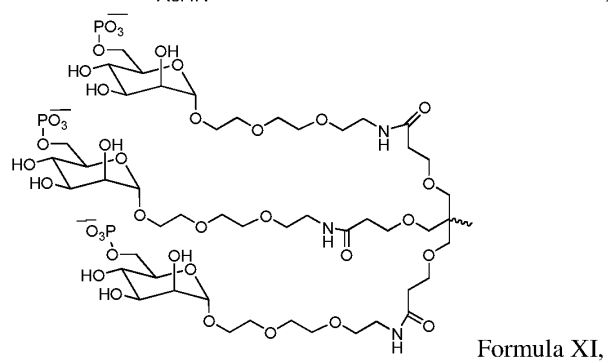
Formula V,

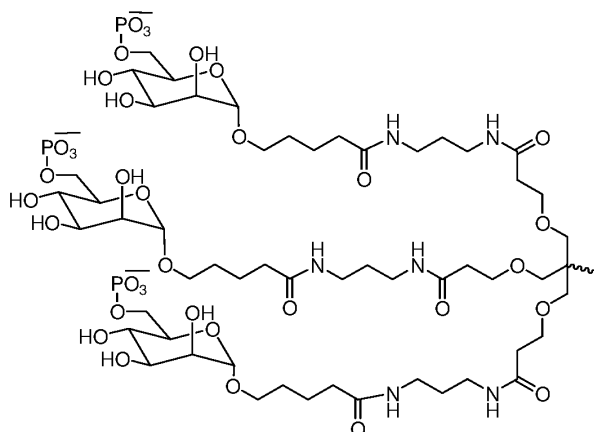


Formula VI,

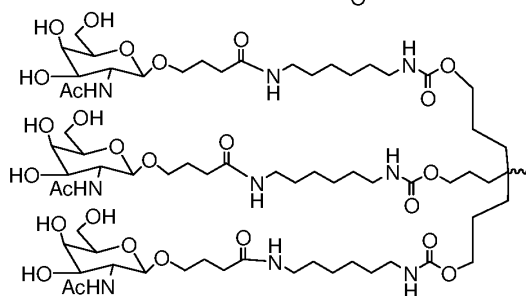


Formula VII,

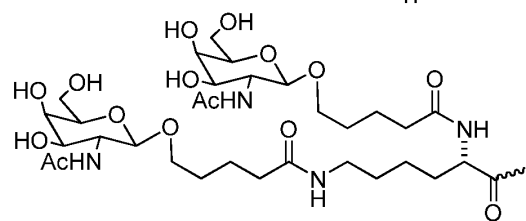




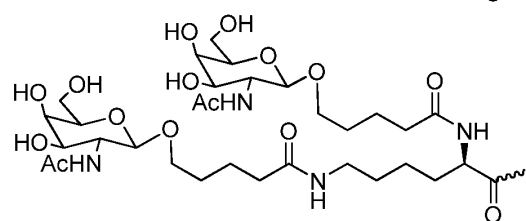
Formula XII,



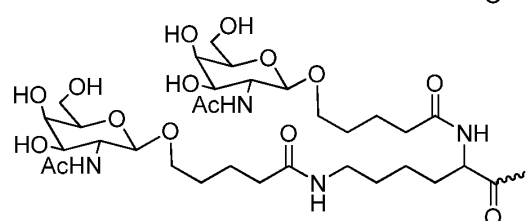
Formula XIII,



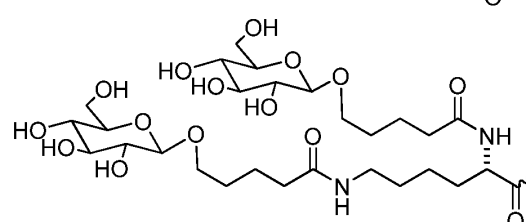
Formula XIV,



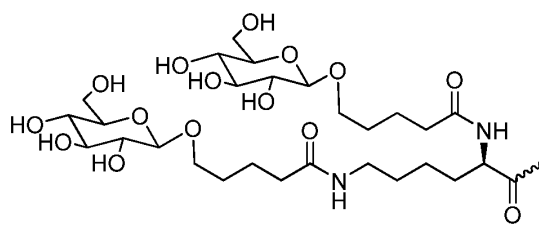
Formula XV,



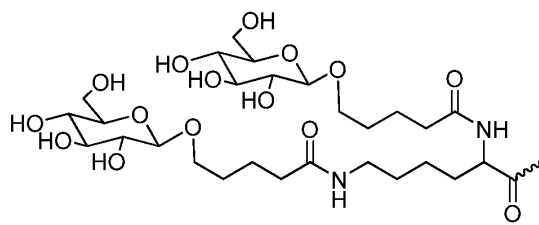
Formula XVI,



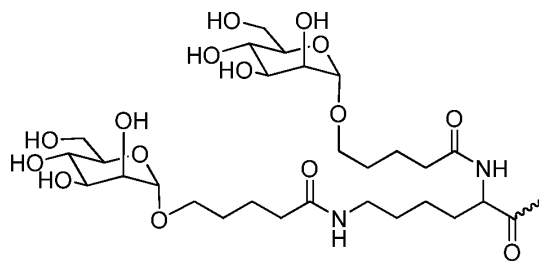
Formula XVII,



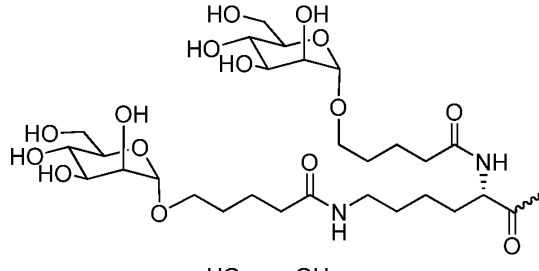
Formula XVIII,



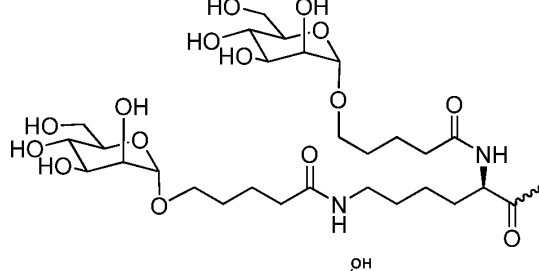
Formula XIX,



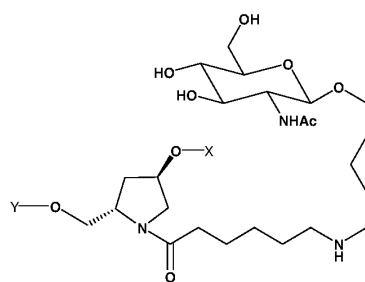
Formula XX,



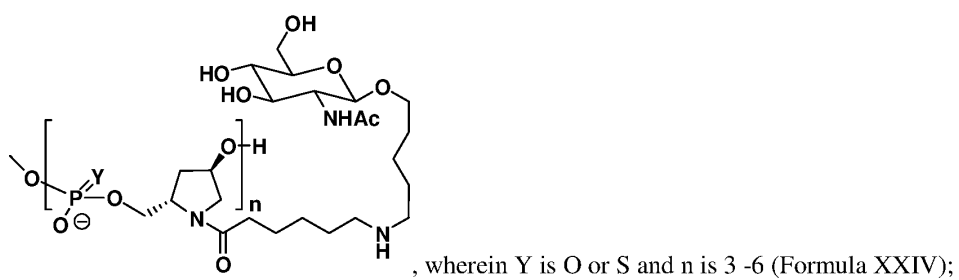
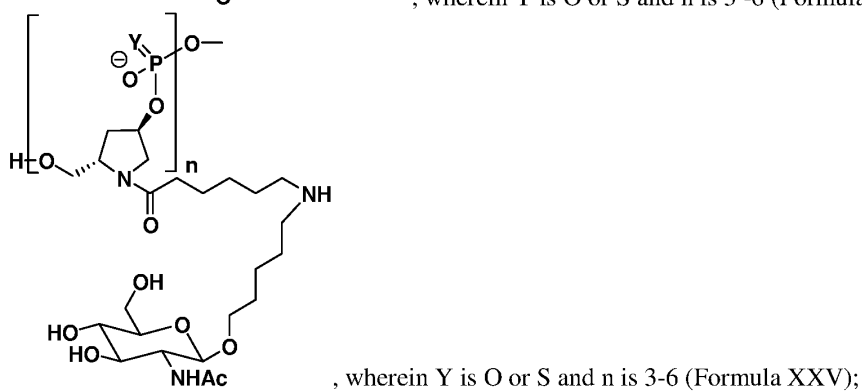
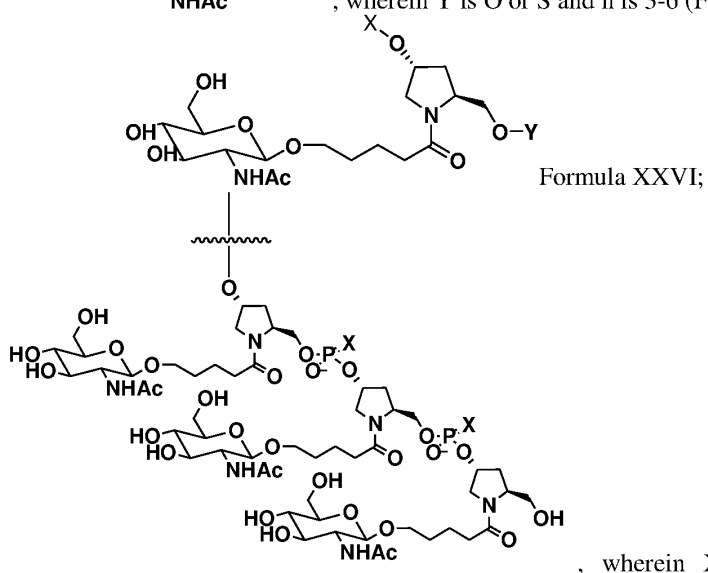
Formula XXI,



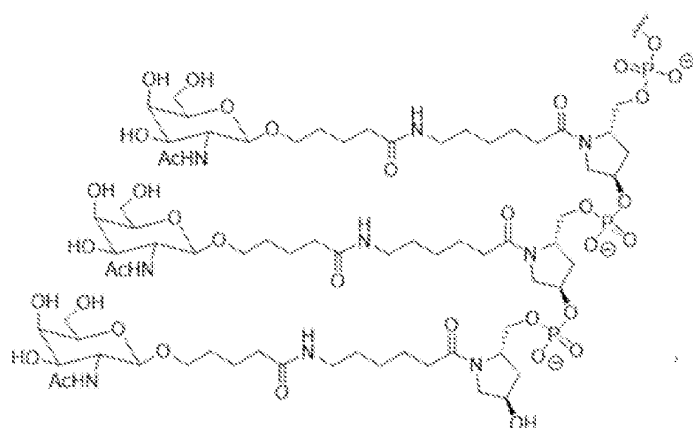
Formula XXII,



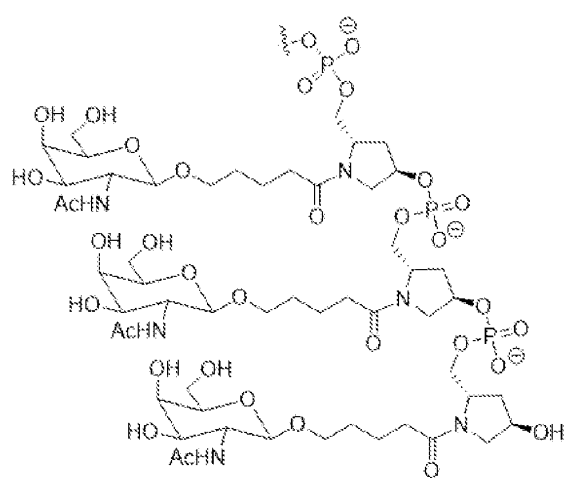
Formula XXIII;



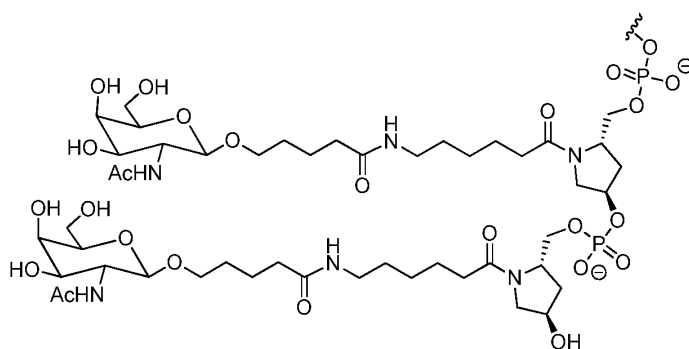
5 XXVII);



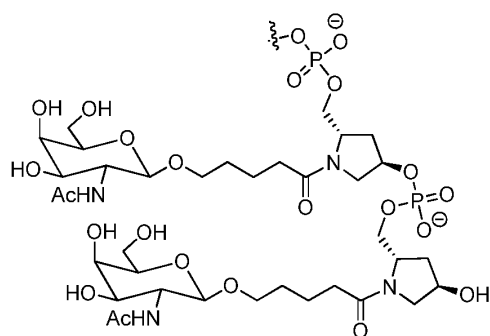
Formula XXVIII:



Formula XXIX:

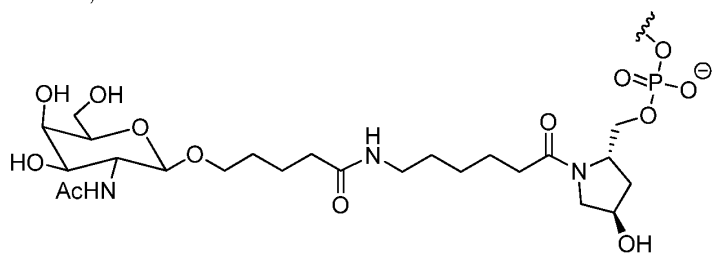


Formula XXX;

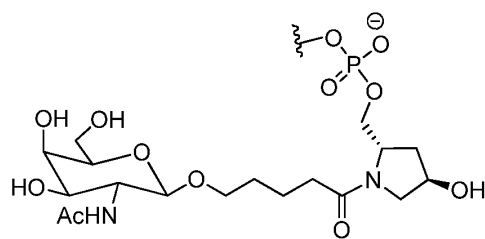


Formula XXXI;

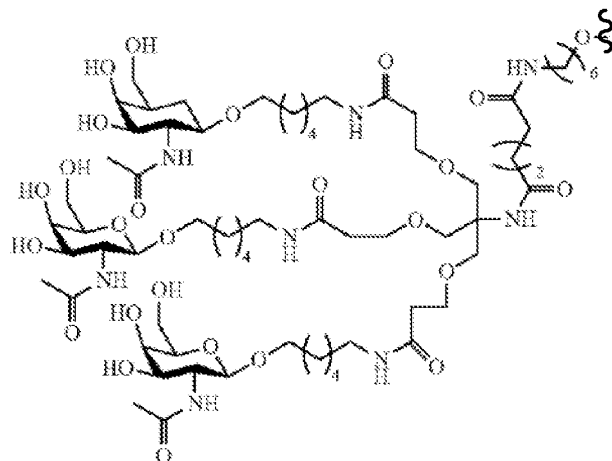
Formula XXXII;



, and

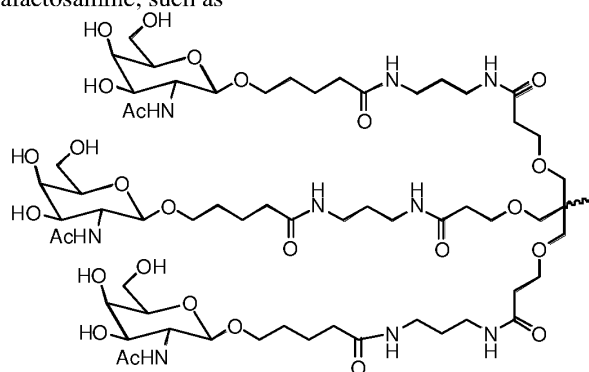


Formula XXXIII.



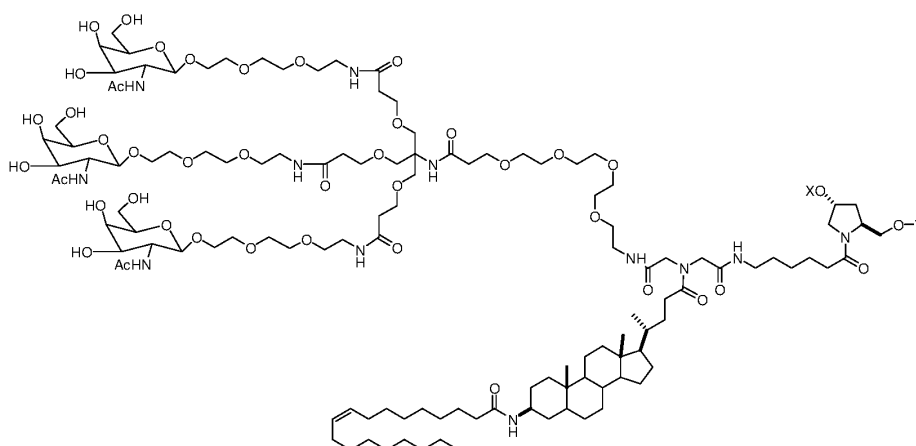
(Formula XXXIV)

In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In certain embodiments, the monosaccharide is an N-acetylgalactosamine, such as



Formula II.

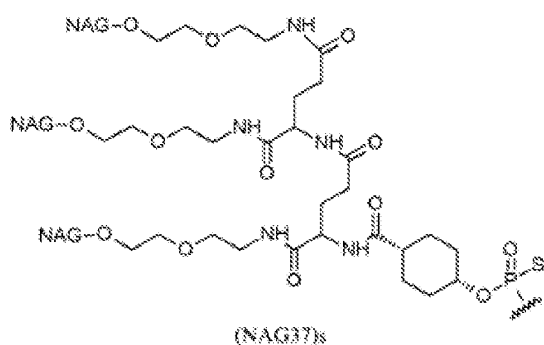
Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI),

when one of X or Y is an oligonucleotide, the other is a hydrogen.

- In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



- In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands, even if such GalNAc ligands are currently projected to be of limited value for the preferred intrathecal/CNS delivery route(s) of the instant disclosure.

- In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker.

- In one embodiment, the double stranded RNAi agents of the invention comprise one or more GalNAc or GalNAc derivative attached to the iRNA agent. The GalNAc may be attached to any nucleotide *via* a linker on the sense strand or antisense strand. The GalNAc may be attached to the 5'-end of the sense strand, the 3' end of the sense strand, the 5'-end of the antisense strand, or the 3' –

end of the antisense strand. In one embodiment, the GalNAc is attached to the 3' end of the sense strand, *e.g.*, *via* a trivalent linker.

In other embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of linkers, *e.g.*, monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention is part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

Additional carbohydrate conjugates and linkers suitable for use in the present invention include those described in WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

D. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₈, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R₈ is hydrogen, acyl, aliphatic or substituted aliphatic. In certain embodiments, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a preferred pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in

whole animals. In preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

5 *i. Redox cleavable linking groups*

In certain embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable “reductively cleavable linking group,” or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

In certain embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Preferred embodiments are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O-, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

In certain embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups

include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula $-C=NN-$, $C(O)O$, or $-OC(O)$. A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

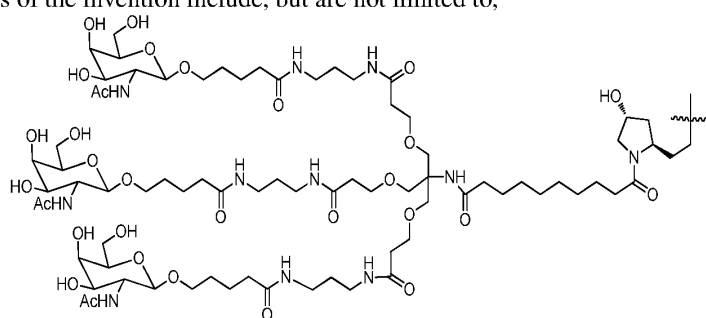
iv. *Ester-based cleavable linking groups*

In certain embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula $-C(O)O-$, or $-OC(O)-$. These candidates can be evaluated using methods analogous to those described above.

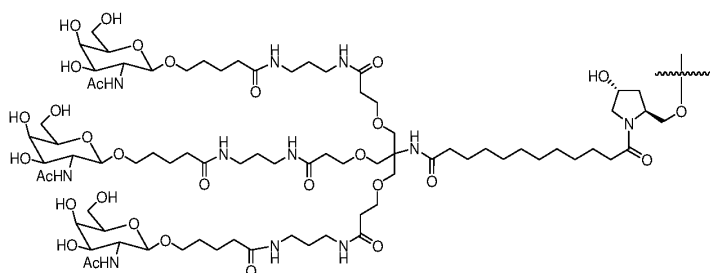
v. *Peptide-based cleavable linking groups*

In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group ($-C(O)NH-$). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula $-NHCHRAC(O)NHCHRBC(O)-$, where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

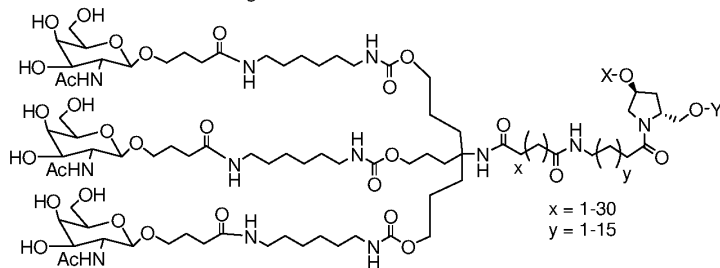
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



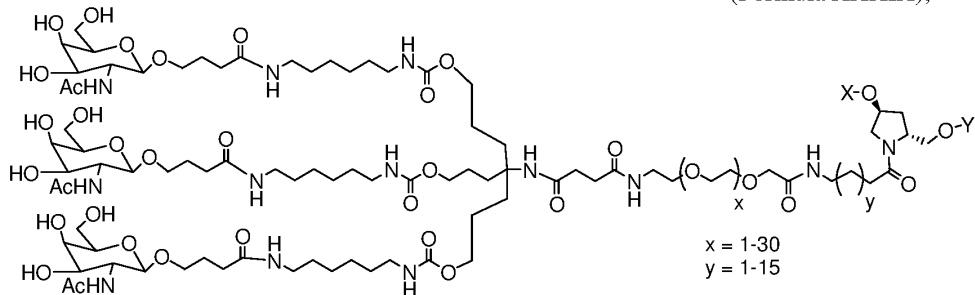
(Formula XXXVII),



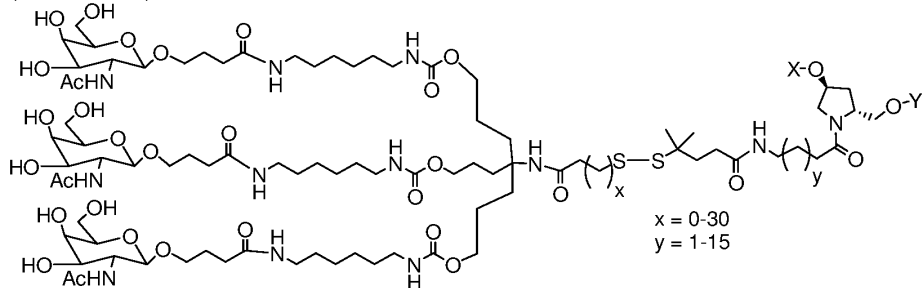
(Formula XXXVIII),



(Formula XXXIX),

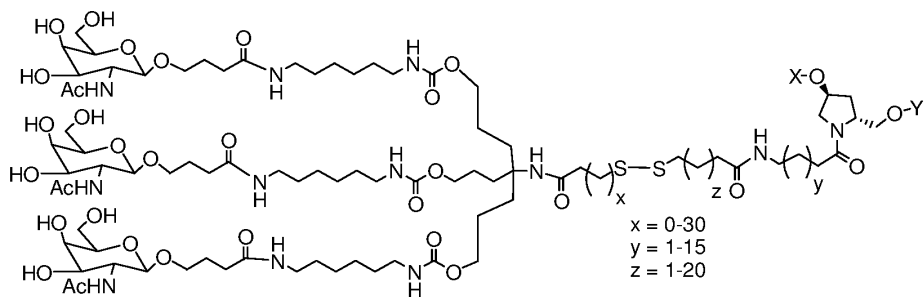


(Formula XL),

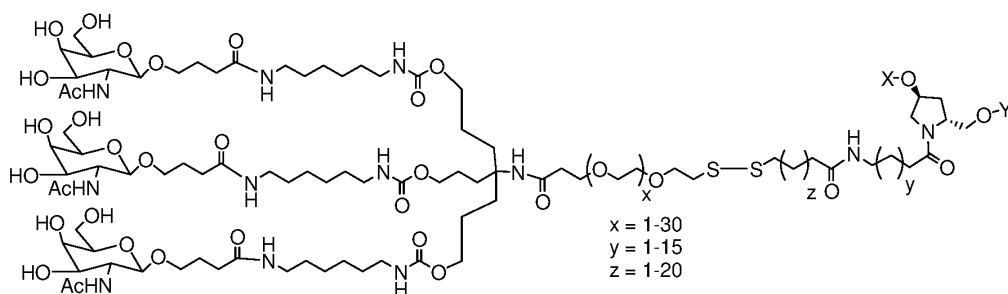


5

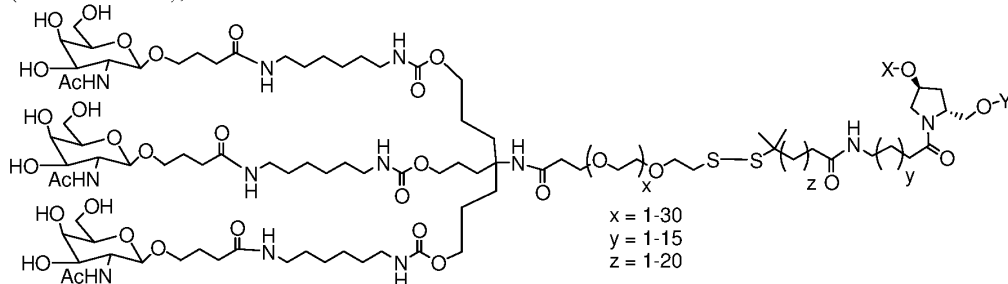
(Formula XLI),



(Formula XLII),



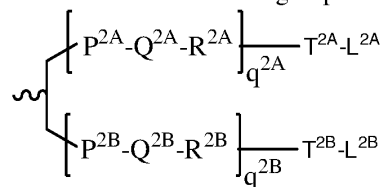
(Formula XLIII), and



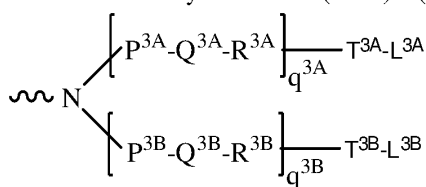
(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

- 5 In certain embodiments of the compositions and methods of the invention, a ligand is one or more “GalNAc” (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

In certain embodiments, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

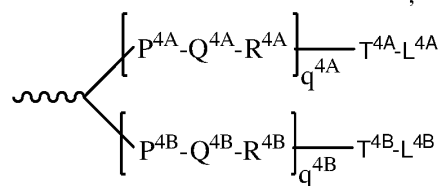


Formula XLV

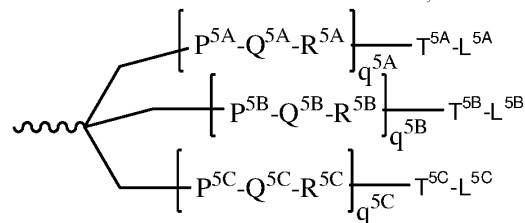


Formula XLVI

10



, Formula XLVII



or

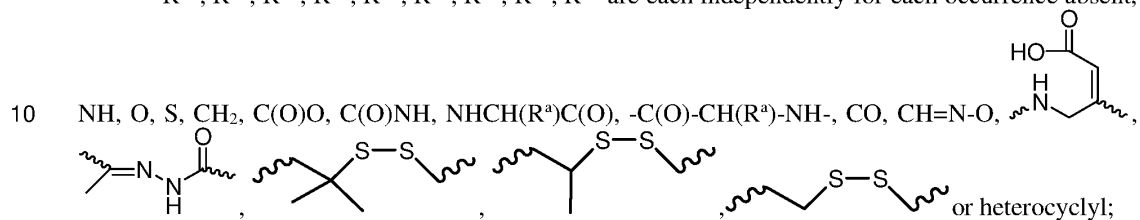
; Formula XLVIII

wherein q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

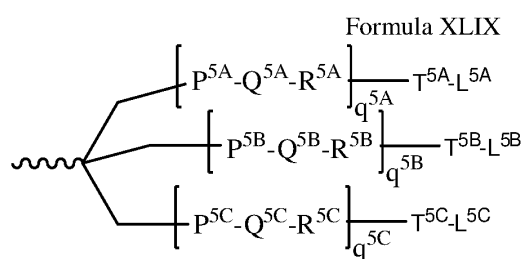
5 $P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{5A}, T^{5B}, T^{5C}$ are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH₂, CH₂NH or CH₂O;

$Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C}$ are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO₂, N(R^N), C(R')=C(R''), C≡C or C(O);

$R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C}$ are each independently for each occurrence absent,



$L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B}$ and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating
15 GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):



wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

20 Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730;
25 5,552,538; 5,578,717; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142;
30 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928; 5,688,941; 6,294,664; 6,320,017;

6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are
5 chimeric compounds.

“Chimeric” iRNA compounds or “chimeras,” in the context of this invention, are iRNA compounds, preferably dsRNA agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These
10 iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase
15 H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al.*, *Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al.*,
25 *Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10:111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-
30 di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating

reagents. The conjugation reaction can be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

5 V. Delivery of an RNAi Agent of the Disclosure

The delivery of an RNAi agent of the disclosure to a cell *e.g.*, a cell within a subject, such as a human subject (*e.g.*, a subject in need thereof, such as a subject having a MAPT-associated disorder, for example, Alzheimer's disease, FTD, PSP, or another tauopathy), can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an RNAi agent of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an RNAi agent, *e.g.*, a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the RNAi agent. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an RNAi agent of the disclosure (see *e.g.*, Akhtar S. and Julian RL., (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider in order to deliver an RNAi agent include, for example, biological stability of the delivered agent, prevention of non-specific effects, and accumulation of the delivered agent in the target tissue. The non-specific effects of an RNAi agent can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the RNAi agent to be administered. Several studies have shown successful knockdown of gene products when an RNAi agent is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ. *et al.*, (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ. *et al.* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J. *et al.* (2005) *Mol. Ther.* 11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ. *et al.*, (2006) *Mol. Ther.* 14:343-350; Li, S. *et al.*, (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G. *et al.*, (2004) *Nucleic Acids* 32:e49; Tan, PH. *et al.* (2005) *Gene Ther.* 12:59-66; Makimura, H. *et al.* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al.* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al.* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya, Y., *et al.* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA. *et al.*, (2006) *Mol. Ther.* 14:476-484; Zhang, X. *et al.*, (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V. *et al.*, (2005) *Nat. Med.* 11:50-55). For administering an RNAi agent systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the

dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the RNAi agent to the target tissue and avoid undesirable off-target effects (*e.g.*, without wishing to be bound by theory, use of GNAs as described herein has been identified to destabilize the seed region of a dsRNA, resulting in enhanced preference of such

5 dsRNAs for on-target effectiveness, relative to off-target effects, as such off-target effects are significantly weakened by such seed region destabilization). RNAi agents can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an RNAi agent directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the

10 liver and jejunum (Soutschek, J. *et al.*, (2004) *Nature* 432:173-178). Conjugation of an RNAi agent to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO. *et al.*, (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the RNAi agent can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery

15 systems facilitate binding of molecule RNAi agent (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an RNAi agent by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an RNAi agent, or induced to form a vesicle or micelle (see *e.g.*, Kim SH. *et al.*, (2008) *Journal of Controlled Release* 129(2):107-116) that encases an RNAi agent. The formation of vesicles or micelles further prevents degradation of the

20 RNAi agent when administered systemically. Methods for making and administering cationic- RNAi agent complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al.* (2003) *J. Mol. Biol* 327:761-766; Verma, UN. *et al.*, (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al.* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of RNAi

25 agents include DOTAP (Sorensen, DR., *et al.* (2003), *supra*; Verma, UN. *et al.*, (2003), *supra*), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS. *et al.*, (2006) *Nature* 441:111-114), cardiolipin (Chien, PY. *et al.*, (2005) *Cancer Gene Ther.* 12:321-328; Pal, A. *et al.*, (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME. *et al.*, (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA. *et al.*, (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H. *et al.*, (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an RNAi agent forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of RNAi agents and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

35 Certain aspects of the instant disclosure relate to a method of reducing the expression of a MAPT target gene in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is an extrahepatic cell, optionally a CNS cell. In other embodiment, the cell is a hepatic cell.

Another aspect of the disclosure relates to a method of reducing the expression of a MAPT target gene in a subject, comprising administering to the subject the double-stranded RNAi agent of the disclosure.

Another aspect of the disclosure relates to a method of treating a subject having a CNS disorder (neurodegenerative disorder), comprising administering to the subject a therapeutically effective amount of the double-stranded MAPT-targeting RNAi agent of the disclosure, thereby treating the subject. The neurodegenerative disorder of the subject is associated with an abnormality of MAPT gene encoded protein Tau. The abnormality of MAPT gene encoded protein Tau may result in aggregation of Tau in subject's brain.

Exemplary CNS disorders that can be treated by the method of the disclosure include MAPT-associated disease CNS disorder such as tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

In one embodiment, the double-stranded RNAi agent is administered intrathecally. By intrathecal administration of the double-stranded RNAi agent, the method can reduce the expression of a MAPT target gene in a brain (*e.g.*, striatum) or spine tissue, for instance, cortex, cerebellum, cervical spine, lumbar spine, and thoracic spine, immune cells such as monocytes and T-cells.

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to modified siRNA compounds. It may be understood, however, that these formulations, compositions and methods can be practiced with other siRNA compounds, *e.g.*, unmodified siRNA compounds, and such practice is within the disclosure. A composition that includes an RNAi agent can be delivered to a subject by a variety of routes. Exemplary routes include: intrathecal, intravenous, topical, rectal, anal, vaginal, nasal, pulmonary, and ocular.

The RNAi agents of the disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of RNAi agent 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.

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, vaginal, rectal, intranasal, transdermal),
5 intrathecal, oral, or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For example, to target neural or spinal tissue, intrathecal injection would be a logical choice. Lung cells might be targeted by administering the RNAi agent in aerosol form. The vascular endothelial cells could be
10 targeted by coating a balloon catheter with the RNAi agent and mechanically introducing the RNA.

Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated
15 condoms, gloves and the like may also be useful.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate
20 and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents can be added.

Compositions for intrathecal or intraventricular administration may include sterile aqueous
25 solutions which may also contain buffers, diluents, and other suitable additives.

Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes may be controlled to render the preparation isotonic.

In one embodiment, the administration of the siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, composition is parenteral, *e.g.*, intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral, or ocular. Administration can be provided by the subject or by another
30 person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

A. *Intrathecal Administration.*

In one embodiment, the double-stranded RNAi agent is delivered by intrathecal injection (*i.e.*, injection into the spinal fluid which bathes the brain and spinal cord tissue). Intrathecal injection of RNAi agents into the spinal fluid can be performed as a bolus injection or *via* minipumps which can be implanted beneath the skin, providing a regular and constant delivery of siRNA into the spinal fluid. The circulation of the spinal fluid from the choroid plexus, where it is produced, down around the spinal chord and dorsal root ganglia and subsequently up past the cerebellum and over the cortex to the arachnoid granulations, where the fluid can exit the CNS, that, depending upon size, stability, and solubility of the compounds injected, molecules delivered intrathecally could hit targets throughout the entire CNS.

In some embodiments, the intrathecal administration is *via* a pump. The pump may be a surgically implanted osmotic pump. In one embodiment, the osmotic pump is implanted into the subarachnoid space of the spinal canal to facilitate intrathecal administration.

In some embodiments, the intrathecal administration is *via* an intrathecal delivery system for a pharmaceutical including a reservoir containing a volume of the pharmaceutical agent, and a pump configured to deliver a portion of the pharmaceutical agent contained in the reservoir. More details about this intrathecal delivery system may be found in WO 2015/116658, which is incorporated by reference in its entirety.

The amount of intrathecally injected RNAi agents may vary from one target gene to another target gene and the appropriate amount that has to be applied may have to be determined individually for each target gene. Typically, this amount ranges from 10 µg to 2 mg, preferably 50 µg to 1500 µg, more preferably 100 µg to 1000 µg.

B. *Vector encoded RNAi agents of the Disclosure*

RNAi agents targeting the MAPT gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; WO 00/22113, WO 00/22114, and US 6,054,299). Expression is preferably sustained (months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

The individual strand or strands of an RNAi agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively, each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

RNAi agent expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be

used to produce recombinant constructs for the expression of an RNAi agent as described herein. Delivery of RNAi agent expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

5 Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors
10 or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an RNAi agent will generally require
15 regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the RNAi agent in target cells. Other aspects to consider for vectors and constructs are known in the art.

VI. Pharmaceutical Compositions of the Invention

20 The present disclosure also includes pharmaceutical compositions and formulations which include the RNAi agents of the disclosure. In one embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent are useful for treating a disease or disorder associated with the expression or activity of MAPT, *e.g.*, MAPT-associated disease.

25 In some embodiments, the pharmaceutical composition of the invention is the dsRNA agent for selective inhibition of exon 10-containing MAPT transcripts.

 In some embodiments, the pharmaceutical compositions of the invention are sterile. In another embodiment, the pharmaceutical compositions of the invention are pyrogen free.

30 Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by intravenous (IV), intramuscular (IM), or for subcutaneous (subQ) delivery. Another example is compositions that are formulated for direct delivery into the CNS, *e.g.*, by intrathecal or intravitreal routes of injection, optionally by infusion into the brain (*e.g.*, striatum), such as by continuous pump infusion.

35 The pharmaceutical compositions of the disclosure may be administered in dosages sufficient to inhibit expression of a MAPT gene. In general, a suitable dose of an RNAi agent of the disclosure will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day.

A repeat-dose regimen may include administration of a therapeutic amount of an RNAi agent on a regular basis, such as monthly to once every six months. In certain embodiments, the RNAi agent is administered about once per quarter (*i.e.*, about once every three months) to about twice per year.

After an initial treatment regimen (*e.g.*, loading dose), the treatments can be administered on a
5 less frequent basis.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 1, 2, 3, or 4 or more month intervals. In some embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per month. In other embodiments of the disclosure, a single dose of
10 the pharmaceutical compositions of the disclosure is administered once per quarter to twice per year.

The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include
15 a single treatment or a series of treatments.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as ALS and FTD that would benefit from reduction in the expression of MAPT. Such models can be used for *in vivo* testing of RNAi agents, as well as for determining a therapeutically effective dose. Suitable rodent models are known in the art and include, for example,
20 those described in, for example, Cepeda, *et al.* (*ASN Neuro* (2010) 2(2):e00033) and Pouladi, *et al.* (*Nat Reviews* (2013) 14:708).

The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or
25 insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

The RNAi agents can be delivered in a manner to target a particular tissue, such as the CNS
30 (*e.g.*, neuronal, glial or vascular tissue of the brain).

Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical
35 formulations include those in which the RNAi agents featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*,

dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). RNAi agents featured in the disclosure can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi agents can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C₁₋₂₀ alkyl ester (e.g., isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in US 6,747,014, which is incorporated herein by reference.

A. *RNAi Agent Formulations Comprising Membranous Molecular Assemblies*

An RNAi agent for use in the compositions and methods of the disclosure can be formulated for delivery in a membranous molecular assembly, e.g., a liposome or a micelle. As used herein, the term “liposome” refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, e.g., one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the RNAi agent composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the RNAi agent composition, although in some examples, it may. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the RNAi agent are delivered into the cell where the RNAi agent can specifically bind to a target RNA and can mediate RNAi. In some cases, the liposomes are also specifically targeted, e.g., to direct the RNAi agent to particular cell types.

A liposome containing an RNAi agent can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The RNAi agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the RNAi agent and condense around the RNAi agent to form a liposome. After condensation, the detergent is removed, e.g., by dialysis, to yield a liposomal preparation of RNAi agent.

If necessary a carrier compound that assists in condensation can be added during the condensation reaction, e.g., by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (e.g., spermine or spermidine). pH can also be adjusted to favor condensation.

Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, *e.g.*, WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417; United States Patent No. 4,897,355; United States Patent No. 5,171,678; Bangham *et al.*, (1965) *M. Mol. Biol.* 23:238; Olson *et al.*, (1979) *Biochim. Biophys. Acta* 557:9; Szoka *et al.*, (1978) *Proc. Natl. Acad. Sci.* 75: 4194; Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169; Kim *et al.*, (1983) *Biochim. Biophys. Acta* 728:339; and Fukunaga *et al.*, (1984) *Endocrinol.* 115:757. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer *et al.*, (1986) *Biochim. Biophys. Acta* 858:161. Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169. These methods are readily adapted to packaging RNAi agent preparations into liposomes.

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.* (1987) *Biochem. Biophys. Res. Commun.*, 147:980-985).

Liposomes, which are pH-sensitive or negatively charged, entrap nucleic acids rather than complex with them. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH sensitive liposomes have been used to deliver nucleic acids encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.* (1992) *Journal of Controlled Release*, 19:269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid or phosphatidylcholine or cholesterol.

Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include United States Patent No. 5,283,185; United States Patent No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, (1994) *J. Biol. Chem.* 269:2550; Nabel, (1993) *Proc. Natl. Acad. Sci.* 90:11307; Nabel, (1992) *Human Gene Ther.* 3:649; Gershon, (1993) *Biochem.* 32:7143; and Strauss, (1992) *EMBO J.* 11:417.

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporine A into different layers of the skin (Hu *et al.*, (1994) *S.T.P. Pharma. Sci.*, 4(6):466).

Liposomes also include “sterically stabilized” liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, (1987) *FEBS Letters*, 223:42; Wu *et al.*, (1993) *Cancer Research*, 53:3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, (1987), 507:64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, (1988), 85:6949). United States Patent No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. United States Patent No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al.*).

In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages *in vivo* and can be used to deliver RNAi agents to macrophages.

Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated RNAi agents in their internal compartments from metabolism and degradation (Rosoff, in “Pharmaceutical Dosage Forms,” Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of RNAi agent (see, *e.g.*, Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417, and United States Patent No.4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ (Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoyleamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPEs") (see, *e.g.*, United States Patent No. 5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., (1991) *Biochim. Biophys. Res. Commun.* 179:280). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, (1991) *Biochim. Biophys. Acta* 1065:8). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration; liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells and also to enhance the penetration of RNAi agent into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied

topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al.*, (1992) *Journal of Drug Targeting*, vol. 2,405-410 and du Plessis *et al.*, (1992) *Antiviral Research*, 18:259-265; Mannino, R. J. and Fould-Fogerite, S., (1998) *Biotechniques* 6:682-690; Itani, T. *et al.*, (1987) *Gene* 56:267-276; Nicolau, C. *et al.* (1987) *Meth. Enzymol.* 149:157-176; 5 Straubinger, R. M. and Papahadjopoulos, D. (1983) *Meth. Enzymol.* 101:512-527; Wang, C. Y. and Huang, L., (1987) *Proc. Natl. Acad. Sci. USA* 84:7851-7855).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome I (glyceryl 10 dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with RNAi agent are useful for treating a dermatological disorder.

Liposomes that include RNAi agents can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the 15 liposome. For example, transfersomes are a type of deformable liposomes. Transfersomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the 20 influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transfersomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

Other formulations amenable to the present disclosure are described in United States provisional application serial Nos. 61/018,616, filed January 2, 2008; 61/018,611, filed January 2, 25 2008; 61/039,748, filed March 26, 2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May 8, 2008. PCT application number PCT/US2007/080331, filed October 3, 2007, also describes formulations that are amenable to the present disclosure.

Transfersomes, yet another type of liposomes, are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can be described as lipid droplets 30 which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.*, they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have 35 been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

Surfactants find wide application in formulations such as those described herein, particularly in emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the

use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

5 If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated
10 esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

 If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl
15 lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

 If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water,
20 the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

 If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

25 The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

 The RNAi agent for use in the methods of the disclosure can also be provided as micellar formulations. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of
30 the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

 A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, an alkali metal C₈ to C₂₂ alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin,
35 hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues

thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

5 In one method a first micellar composition is prepared which contains the siRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the siRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle
10 forming compounds, with vigorous mixing.

Phenol or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

15 For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.*, there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.*, through a metered valve. The
20 dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2 tetrafluoroethane) may be used.

The specific concentrations of the essential ingredients can be determined by relatively
25 straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, *e.g.*, at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

B. Lipid particles

RNAi agents, *e.g.*, dsRNAs of in the disclosure may be fully encapsulated in a lipid
30 formulation, *e.g.*, a LNP, or other nucleic acid-lipid particle.

As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (*i.v.*) injection and accumulate at distal sites (*e.g.*, sites
35 physically separated from the administration site). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the

nucleic acid- lipid particles of the present disclosure are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; United States Patent Publication No. 2010/0324120 and WO 96/40964.

5 In one embodiment, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

Certain specific LNP formulations for delivery of RNAi agents have been described in the art, including, *e.g.*, “LNP01” formulations as described in, *e.g.*, WO 2008/042973, which is hereby
10 incorporated by reference.

Additional exemplary lipid-dsRNA formulations are identified in the Table 1 below.

Table 1

	Ionizable/Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
SNALP-1	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
2-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1

LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyldidodecan-2-ol (Tech G1)	Tech G1/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1

LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine; DPPC: dipalmitoylphosphatidylcholine; PEG-DMG: PEG-didimristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000); PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000); PEG-cDMA: PEG-carbamoyl-1,2-dimristyloxypropylamine (PEG with avg mol wt of 2000) and SNALP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in WO 2009/127060, which is hereby incorporated by reference.

XTC comprising formulations are described in WO 2010/088537, the entire contents of which are hereby incorporated herein by reference.

MC3 comprising formulations are described, *e.g.*, in United States Patent Publication No. 2010/0324120, the entire contents of which are hereby incorporated by reference.

ALNY-100 comprising formulations are described in WO 2010/054406, the entire contents of which are hereby incorporated herein by reference.

C12-200 comprising formulations are described in WO 2010/129709, the entire contents of which are hereby incorporated herein by reference.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitabets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the disclosure are administered in conjunction with one or more penetration enhancer surfactants and chelators. Suitable surfactants include fatty acids or esters or salts thereof, bile acids or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.*, sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the disclosure can be delivered orally, in

granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, 5 pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (e.g., p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, 10 DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, U.S. 2003/0027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

15 Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present disclosure include, but are not limited to, 20 solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the brain when treating MAPT associated diseases or disorders.

The pharmaceutical formulations of the present disclosure, which can conveniently be 25 presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

30 The compositions of the present disclosure can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present disclosure can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium 35 carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

C. Additional Formulations

i. Emulsions

The compositions of the present disclosure can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of

droplets usually exceeding 0.1 μ m in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in
5 Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed
10 with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional
15 components in addition to the dispersed phases, and the active drug which can be present as a solution in either aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w)
20 emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or
25 discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion can be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that can be incorporated into either phase of the emulsion. Emulsifiers can broadly be classified into four
30 categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

35 Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y.,

volume 1, p. 285; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants can be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (see *e.g.*, Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgit, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that can readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used can be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents

such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations *via* dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. *Microemulsions*

In one embodiment of the present disclosure, the compositions of RNAi agents and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically, microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared *via* a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used, and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in

Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385-1390; Ritschel, Meth. Find. Exp. Clin. Pharmacol., 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385; Ho *et al.*, J. Pharm. Sci., 1996, 85, 138-143). Often microemulsions can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or RNAi agents. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present disclosure will facilitate the increased systemic absorption of RNAi agents and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of RNAi agents and nucleic acids.

Microemulsions of the present disclosure can also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the RNAi agents and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure can be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 92). Each of these classes has been discussed above.

iii. *Microparticles*

An RNAi agent of the disclosure may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. *Penetration Enhancers*

In one embodiment, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly RNAi agents, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

Surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of RNAi agents through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, J. Pharm. Pharmacol., 1988, 40, 252).

Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C₁₋₂₀ alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*)

(see *e.g.*, Touitou, E., *et al.* Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri *et al.*, J. Pharm. Pharmacol., 1992, 44, 651-654).

- 5 The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers.
- 10 Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucolic acid (sodium glucolate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita *et al.*, J. Pharm. Sci., 1990, 79, 579-583).

- 25 Chelating agents, as used in connection with the present disclosure, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of RNAi agents through the mucosa is enhanced. With regards to their use as penetration enhancers in the present disclosure, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, J. Chromatogr., 1993, 618, 315-339).
- 30 Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of beta-diketones (enamines)(see *e.g.*, Katdare, A. *et al.*, Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Buur *et al.*, J. Control Rel., 1990, 14, 43-51).
- 35

As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of RNAi agents through the alimentary mucosa (see *e.g.*,

Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacycloalkanone derivatives (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, J. Pharm. Pharmacol., 1987, 39, 621-626).

Agents that enhance uptake of RNAi agents at the cellular level can also be added to the pharmaceutical and other compositions of the present disclosure. For example, cationic lipids, such as lipofectin (Junichi *et al.*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (WO 97/30731), are also known to enhance the cellular uptake of dsRNAs.

Other agents can be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

v. *Excipients*

In contrast to a carrier compound, a “pharmaceutical carrier” or “excipient” is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc.*).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present disclosure. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vi. *Other Components*

5 The compositions of the present disclosure can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the
10 present disclosure, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present disclosure. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers,
15 colorings, flavorings or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

20 In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more RNAi agents and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating a MAPT-associated disorder. Examples of such agents include, but are not limited to, cholinesterase inhibitors, memantine, monoamine inhibitors, reserpine, anticonvulsants, antipsychotic agents, and antidepressants.

25 Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit high therapeutic indices are preferred.

30 The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the disclosure lies generally within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the disclosure, the
35 therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC₅₀ (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such

information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the RNAi agents featured in the disclosure can be administered in combination with other known agents effective in treatment of pathological processes mediated by nucleotide repeat expression. In any event, the administering physician can adjust the amount and timing of RNAi agent administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VII. Kits

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof).

Such kits include one or more dsRNA agent(s) and instructions for use, *e.g.*, instructions for administering a prophylactically or therapeutically effective amount of a dsRNA agent(s). The dsRNA agent may be in a vial or a pre-filled syringe. The kits may optionally further comprise means for administering the dsRNA agent (*e.g.*, an injection device, such as a pre-filled syringe or an intrathecal pump), or means for measuring the inhibition of MAPT (*e.g.*, means for measuring the inhibition of MAPT mRNA, Tau, and/or MAPT activity). Such means for measuring the inhibition of MAPT may comprise a means for obtaining a sample from a subject, such as, *e.g.*, a CSF and/or plasma sample. The kits of the invention may optionally further comprise means for determining the therapeutically effective or prophylactically effective amount.

In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

VIII. Methods for Inhibiting MAPT Expression

The present disclosure also provides methods of inhibiting expression of a MAPT gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNAi agent, in an amount effective to inhibit expression and/or activity of MAPT in the cell, thereby inhibiting expression and/or activity of MAPT in the cell. The present disclosure also provides methods of selective inhibition of exon 10-containing MAPT transcripts in a cell. The methods include contacting

the cell with a dsRNA agent of the present disclosure, or a pharmaceutical composition of the present disclosure, thereby selectively degrading exon 10-containing MAPT transcripts in the cell. In certain embodiments, the cell is within a subject. In certain embodiments, the subject is a human. In certain embodiments, the subject has a MAPT-associated disorder. In certain embodiments, the MAPT-associated disorder is a neuro-degenerative disorder. In certain embodiments, the neurodegenerative disorder is associated with an abnormality of MAPT gene encoded protein Tau. In certain embodiments, the abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain.

In certain embodiments of the disclosure, MAPT expression and/or activity is inhibited by at least 30% preferentially in CNS (*e.g.*, brain) cells. In specific embodiments, MAPT expression and/or activity is inhibited by at least 30%. In certain embodiments, Tau protein level in serum of the subject is inhibited by at least 30%. In certain other embodiments of the disclosure, MAPT expression and/or activity is inhibited by at least 30% preferentially in hepatocytes.

Contacting of a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible. A108868_1030US_P2_Specification

Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition. In certain embodiments, a level of inhibition, *e.g.*, for an RNAi agent of the instant disclosure, can be assessed in cell culture conditions, *e.g.*, wherein cells in cell culture are transfected *via* LipofectamineTM-mediated transfection at a concentration in the vicinity of a cell of 10 nM or less, 1 nM or less, *etc.* Knockdown of a given RNAi agent can be determined *via* comparison of pre-treated levels in cell culture versus post-treated levels in cell culture, optionally also comparing against cells treated in parallel with a scrambled or other form of control RNAi agent. Knockdown in cell culture of, *e.g.*, at least about 30%, can thereby be identified as indicative of "inhibiting" or "reducing," "downregulating" or "suppressing", *etc.* having occurred. It is expressly contemplated that assessment of targeted mRNA or encoded protein levels (and therefore an extent of "inhibiting", *etc.* caused by an RNAi agent of the disclosure) can also be assessed in *in vivo* systems for the RNAi agents of the instant disclosure, under properly controlled conditions as described in the art.

The phrase "inhibiting MAPT," "inhibiting expression of a MAPT gene" or "inhibiting expression of MAPT," as used herein, includes inhibition of expression of any MAPT gene (such as, *e.g.*, a mouse MAPT gene, a rat MAPT gene, a monkey MAPT gene, or a human MAPT gene) as well as variants or mutants of a MAPT gene that encode a Tau. Thus, the MAPT gene may be a wild-type

MAPT gene, a mutant MAPT gene, or a transgenic MAPT gene in the context of a genetically manipulated cell, group of cells, or organism.

“Inhibiting expression of a MAPT gene” includes any level of inhibition of a MAPT gene, *e.g.*, at least partial suppression of the expression of a MAPT gene, such as an inhibition by at least about 25%. In certain embodiments, inhibition is at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, or at least about 99%, relative to a control level. MAPT inhibition can be measured using the *in vitro* assay with, *e.g.*, A549 cells and a 10 nM concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure. In some embodiments, MAPT inhibition can be measured using the *in vitro* assay with BE(2)-C cells. In some embodiments, MAPT inhibition can be measured using the *in vitro* assay with Neuro-2a cells. In another embodiment, MAPT inhibition can be measured using the *in vitro* assay with Cos-7 (Dual-Luciferase psiCHECK2 vector). In yet another embodiment, MAPT inhibition can be measured using the *in vitro* assay with primary mouse hepatocytes.

The expression of a MAPT gene may be assessed based on the level of any variable associated with MAPT gene expression, *e.g.*, MAPT mRNA level (*e.g.*, sense mRNA, antisense mRNA, total MAPT mRNA, sense MAPT repeat-containing mRNA, and/or antisense MAPT repeat-containing mRNA) or Tau level (*e.g.*, total Tau, wild-type Tau, or expanded repeat-containing protein), or, for example, the level of sense- or antisense-containing foci and/or the level of aberrant dipeptide repeat protein.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

For example, in some embodiments of the methods of the disclosure, expression of a MAPT gene (*e.g.*, as assessed by sense- or antisense-containing foci and/or aberrant dipeptide repeat protein level) is inhibited by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, or 95%, relative to a control level, or to below the level of detection of the assay. In other embodiments of the methods of the disclosure, expression of a MAPT gene (*e.g.*, as assessed by mRNA or protein expression level) is inhibited by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level. In certain embodiments, the methods include a clinically relevant inhibition of expression of MAPT, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of MAPT.

Inhibition of the expression of a MAPT gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a MAPT gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the disclosure, or by administering

an RNAi agent of the disclosure to a subject in which the cells are or were present) such that the expression of a MAPT gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an RNAi agent or not treated with an RNAi agent targeted to the gene of interest).

- 5 The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \times 100\%$$

In other embodiments, inhibition of the expression of a MAPT gene may be assessed in terms of a reduction of a parameter that is functionally linked to a MAPT gene expression, *e.g.*, Tau expression, sense- or antisense-containing foci and/or the level of aberrant dipeptide repeat protein. MAPT gene silencing may be determined in any cell expressing MAPT, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of MAPT gene may be manifested by a reduction in the level of the Tau protein (or functional parameter, *e.g.*, reduction in microtubule assembly) that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed in a sample derived from a subject). As explained above, for the assessment of mRNA suppression, the inhibition of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells. In some embodiments, the phrase “inhibiting MAPT”, can also refer to the inhibition of Tau protein expression, *e.g.*, at least partial suppression Tau expression, such as an inhibition by at least about 25%. In certain embodiments, inhibition of the MAPT activity is by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, or at least about 99%, relative to a control level. Tau protein levels can be measured using the *in vitro* assay with, *e.g.*, the assay described in (Rubenstein *et al.* (2015) *J. Neurotrauma* 2015 Mar1: 32 (5):342-352; Lim *et al.* (2014) *Comput Struct Biotechnol J.* 2014;12(20-21):7-13). MAPT expression can be measured using the *in vitro* assay with, *e.g.*, the assay described in (Caillet-Boudin *et al.* (2015) *Mol Neurodegener.* 2015; 10:28; Hefti *et al.* (2018) *PLoS ONE* 13(4): e0195771).

A control cell or group of cells that may be used to assess the inhibition of the expression of a MAPT gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

The level of MAPT mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of MAPT in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the MAPT gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasyTM RNA preparation kits (Qiagen®) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR,

RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis. Strand specific MAPT mRNAs may be detected using the quantitative RT-PCR and or droplet digital PCR methods described in, for example, Jiang, *et al. supra*, Lagier-Tourenne, *et al., supra* and Jiang, *et al., supra*. Circulating MAPT mRNA may be detected using methods the described in WO2012/177906, the entire contents of which are hereby incorporated herein by reference.

In some embodiments, the level of expression of MAPT is determined using a nucleic acid probe. The term “probe”, as used herein, refers to any molecule that is capable of selectively binding to a specific MAPT nucleic acid or protein, or fragment thereof. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to MAPT mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of MAPT mRNA.

An alternative method for determining the level of expression of MAPT in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, US Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, US Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the disclosure, the level of expression of MAPT is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System), by a Dual-Glo® Luciferase assay, or by other art-recognized method for measurement of MAPT expression or mRNA level.

The expression level of MAPT mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See US Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by

reference. The determination of MAPT expression level may also comprise using nucleic acid probes in solution.

In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of this PCR method is described and exemplified in the Examples presented herein. Such methods can also be used for the detection of MAPT nucleic acids.

The level of Tau expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like. Such assays can also be used for the detection of proteins indicative of the presence or replication of Tau. Tau protein levels can be measured using the *in vitro* assay with, *e.g.*, the assay described in (Rubenstein *et al.* (2015) *J. Neurotrauma* 2015 Mar1: 32 (5):342-352; Lim *et al.* (2014) *Comput Struct Biotechnol J.* 2014;12(20-21):7-13).

The level of sense- or antisense-containing foci and the level of aberrant dipeptide repeat protein may be assessed using methods well-known to one of ordinary skill in the art, including, for example, fluorescent *in situ* hybridization (FISH), immunohistochemistry and immunoassay (see, *e.g.*, Jiang, *et al. supra*). In some embodiments, the efficacy of the methods of the disclosure in the treatment of a MAPT-associated disease is assessed by a decrease in MAPT mRNA level (*e.g.*, by assessment of a CSF sample and/or plasma sample for MAPT level, by brain biopsy, or otherwise).

In some embodiments of the methods of the disclosure, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of MAPT may be assessed using measurements of the level or change in the level of MAPT mRNA (*e.g.*, sense mRNA, antisense mRNA, total MAPT mRNA), Tau protein (*e.g.*, total Tau protein, wild-type Tau protein), sense-containing foci, antisense-containing foci, aberrant dipeptide repeat protein in a sample derived from a specific site within the subject, *e.g.*, CNS cells. In certain embodiments, the methods include a clinically relevant inhibition of expression of MAPT, *e.g.*, as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of MAPT, such as, for example, stabilization or inhibition of caudate atrophy (*e.g.*, as assessed by volumetric MRI (vMRI)), a stabilization or reduction in neurofilament light chain (NfL) levels in a CSF sample from a subject, a reduction in mutant MAPT mRNA or a cleaved mutant Tau, *e.g.*, full-length mutant MAPT mRNA or protein and a cleaved mutant MAPT mRNA or protein.

As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.*, protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

IX. Methods of Treating or Preventing MAPT-Associated Diseases

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce or inhibit MAPT expression in a cell. The methods include contacting the cell with a dsRNA of the disclosure and maintaining the cell
5 for a time sufficient to obtain degradation of the mRNA transcript of a MAPT gene, thereby inhibiting expression of the MAPT gene in the cell.

In addition, the present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce the level and/or inhibit formation of sense- and antisense-containing foci in a cell. The methods include contacting the
10 cell with a dsRNA of the disclosure, thereby reducing the level of the MAPT sense- and antisense-containing foci in the cell.

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce the level and/or inhibit formation of aberrant dipeptide repeat protein in a cell. The methods include contacting the cell with a dsRNA
15 of the disclosure, thereby reducing the level of the aberrant dipeptide repeat protein in the cell.

Reduction in gene expression, the level of MAPT sense- and antisense-containing foci, and/or aberrant dipeptide repeat protein can be assessed by any methods known in the art. For example, a reduction in the expression of MAPT may be determined by determining the mRNA expression level of MAPT using methods routine to one of ordinary skill in the art, *e.g.*, northern blotting, qRT-PCR;
20 by determining the protein level of MAPT using methods routine to one of ordinary skill in the art, such as western blotting, immunological techniques.

In the methods of the disclosure the cell may be contacted *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject. The subject may be a human. The subject may have a MAPT-associated disorder. The MAPT-associated disorder may be a neurodegenerative disorder. The
25 neurodegenerative disorder of the subject that can be associated with an abnormality of MAPT gene encoded protein Tau. The abnormality of MAPT gene encoded protein Tau may result in aggregation of Tau in subject's brain.

A cell suitable for treatment using the methods of the disclosure may be any cell that expresses a MAPT gene. A cell suitable for use in the methods of the disclosure may be a mammalian cell, *e.g.*, a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a rat cell, or a mouse cell). In one embodiment, the cell
30 is a human cell, *e.g.*, a human CNS cell.

MAPT expression (*e.g.*, as assessed by sense mRNA, antisense mRNA, total MAPT mRNA, total Tau protein) is inhibited in the cell by about 20%, 25%, 30%, 35%, 40%, 45%, or 50% relative
35 to the expression in a control cell. In certain embodiments, MAPT expression is inhibited by at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level.

In preferred embodiments, MAPT expression is inhibited in the cell by at least 30%. In particular embodiments, inhibiting expression of MAPT may decrease Tau protein level in serum of the subject by at least 30%.

Inhibition, as assessed by sense- or antisense-containing foci and/or aberrant dipeptide repeat protein level) is inhibited in the cell by at least 20%, 30%, 40%, preferably at least 50%, 60%, 70%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay.

The *in vivo* methods of the disclosure may include administering to a subject a composition containing an RNAi agent, where the RNAi agent includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the MAPT gene of the mammal to be treated.

When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, intravitreal, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intrathecal injection.

In some embodiments, the administration is *via* a depot injection. A depot injection may release the RNAi agent in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of MAPT, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intracranial, intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the RNAi agent to the CNS.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present disclosure also provides methods for inhibiting the expression of a MAPT gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a MAPT gene in a cell of the mammal, thereby inhibiting expression of the MAPT gene in the cell. Reduction in gene expression can be assessed by any methods known in the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known in the art and by methods, *e.g.* ELISA, described herein. In one

embodiment, a CNS biopsy sample or a cerebrospinal fluid (CSF) sample serves as the tissue material for monitoring the reduction in MAPT gene or protein expression (or of a proxy therefore).

The present disclosure further provides methods of treatment of a subject in need thereof. The treatment methods of the disclosure include administering an RNAi agent of the disclosure to a subject, *e.g.*, a subject that would benefit from inhibition of MAPT expression, such as a subject having a missense and/or deletion mutations in the MAPT gene, in a therapeutically effective amount of an RNAi agent targeting a MAPT gene or a pharmaceutical composition comprising an RNAi agent targeting a MAPT gene.

In addition, the present disclosure provides methods of preventing, treating or inhibiting the progression of a MAPT-associated disease or disorder (*e.g.*, Alzheimer's disease, FTD, PSP, or another tauopathy), in a subject. The methods include administering to the subject a therapeutically effective amount of any of the RNAi agent, *e.g.*, dsRNA agents, or the pharmaceutical composition provided herein, thereby preventing, treating or inhibiting the progression of a MAPT-associated disease or disorder in the subject. A MAPT-associated disease or disorder that can be prevented by the method of the disclosure can be associated with an abnormality of MAPT gene encoded protein Tau. The abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain. The subject may be human. Administration of a dsRNA agent of the disclosure, or a pharmaceutical composition of the disclosure, may cause a decrease in Tau aggregation in the subject's brain.

An RNAi agent of the disclosure may be administered as a "free RNAi agent." A free RNAi agent is administered in the absence of a pharmaceutical composition. The naked RNAi agent may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the RNAi agent can be adjusted such that it is suitable for administering to a subject.

Alternatively, an RNAi agent of the disclosure may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from a reduction or inhibition of MAPT gene expression are those having a MAPT-associated disease. Exemplary MAPT-associated diseases include, but are not limited to, tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

The disclosure further provides methods for the use of an RNAi agent or a pharmaceutical composition thereof, *e.g.*, for treating a subject that would benefit from reduction or inhibition of MAPT expression, *e.g.*, a subject having a MAPT-associated disorder, in combination with other pharmaceuticals or other therapeutic methods, *e.g.*, with known pharmaceuticals or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an RNAi agent targeting MAPT is administered in combination with, *e.g.*, an agent useful in treating a MAPT-associated disorder as described elsewhere herein or as otherwise known in the art. For example, additional agents suitable for treating a subject that would benefit from reduction in MAPT expression, *e.g.*, a subject having a MAPT-associated disorder, may include agents currently used to treat symptoms of MAPT-associated diseases. The RNAi agent and additional therapeutic agents may be administered at the same time or in the same combination, *e.g.*, intrathecally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times or by another method known in the art or described herein.

Exemplary additional therapeutics include, for example, a monoamine inhibitor, *e.g.*, tetrabenazine (Xenazine), deutetabenazine (Austedo), and reserpine, an anticonvulsant, *e.g.*, valproic acid (Depakote, Depakene, Depacon), and clonazepam (Klonopin), an antipsychotic agent, *e.g.*, risperidone (Risperdal), and haloperidol (Haldol), and an antidepressant, *e.g.*, paroxetine (Paxil).

In one embodiment, the method includes administering a composition featured herein such that expression of the target MAPT gene is decreased, for at least one month. In preferred embodiments, expression is decreased for at least 2 months, 3 months, or 6 months.

Preferably, the RNAi agents useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target MAPT gene. Compositions and methods for inhibiting the expression of these genes using RNAi agents can be prepared and performed as described herein.

Administration of the dsRNA according to the methods of the disclosure may result in a reduction of the severity, signs, symptoms, or markers of such diseases or disorders in a patient with a MAPT-associated disorder. By “reduction” in this context is meant a statistically significant or clinically significant decrease in such level. The reduction can be, for example, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% relative to a control level. Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of a MAPT-associated disorder may be assessed, for example, by periodic monitoring of a subject's. Comparisons

of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an RNAi agent targeting MAPT or pharmaceutical composition thereof, “effective against” a MAPT-associated disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating MAPT-associated disorders and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given RNAi agent drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

Alternatively, the efficacy can be measured by a reduction in the severity of disease as determined by one skilled in the art of diagnosis based on a clinically accepted disease severity grading scale. Any positive change resulting in *e.g.*, lessening of severity of disease measured using the appropriate scale, represents adequate treatment using an RNAi agent or RNAi agent formulation as described herein.

In certain embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 200 mg/kg. In other embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 500 mg/kg. In yet other embodiments, subjects can be administered a therapeutic amount of dsRNA of about 500 mg/kg or more.

The RNAi agent can be administered intrathecally, *via* intravitreal injection, or by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. Administration of the RNAi agent can reduce MAPT levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient. In one embodiment, administration of the RNAi agent can reduce MAPT levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least about 25%, such as about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% relative to a control level.

Before administration of a full dose of the RNAi agent, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Alternatively, the RNAi agent can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired, *e.g.*, monthly dose of RNAi agent to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments
5 can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of RNAi agent on a regular basis, such as monthly or extending to once a quarter, twice per year, once per year. In certain embodiments, the RNAi agent is administered about once per month to about once per quarter (*i.e.*, about once every three months).

Unless otherwise defined, all technical and scientific terms used herein have the same
10 meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the RNAi agents and methods featured in the invention, 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
15 specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

An informal Sequence Listing is filed herewith and forms part of the specification as filed.

EXAMPLES

Example 1. RNAi Agent Design, Synthesis, Selection, and *in Vitro* Evaluation

This Example describes methods for the design, synthesis, selection, and *in vitro* evaluation of MAPT RNAi agents.

Source of reagents

Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

Bioinformatics

siRNAs targeting the human MAPT transcripts (Homo sapiens microtubule associated protein tau (MAPT), transcript variant 4, mRNA, NCBI refseqID NM_016841.4; NCBI GeneID: 4137 and Homo sapiens microtubule associated protein tau (MAPT), transcript variant 2, mRNA, NCBI refseqID NM_005910.6; NCBI GeneID: 4137) were designed using custom R and Python scripts. The human NM_016841.4mRNA has a length of 5544 bases. The human NM_005910.6 mRNA has a length of 5639 bases.

Detailed lists of the unmodified MAPT sense and antisense strand nucleotide sequences targeting human MAPT transcript are shown in Tables 3-5, 16, 18, 20, 22, 25 and 27. Detailed lists of the modified MAPT sense and antisense strand nucleotide sequences targeting human MAPT transcript are shown in Table 6-8, 17, 19, 21, 23, 26 and 28.

siRNAs targeting the mouse MAPT transcript (Mus musculus microtubule-associated protein tau (Mapt), mRNA, NCBI refseqID NM_001038609; NCBI GeneID: 17762) were designed using custom R and Python scripts. The mouse NM_001038609.2 mRNA has a length of 5396 bases.

siRNAs targeting the macaque MAPT transcript (Macaca fascicularis microtubule associated protein tau (MAPT), transcript variant X13, NCBI refseqID XM_005584540.1; NCBI GeneID: 102119414) were designed using custom R and Python scripts. The mouse XM_005584540.1 mRNA has a length of 5790 bases.

Detailed lists of the unmodified MAPT sense and antisense strand nucleotide sequences targeting mouse MAPT transcript are shown in Table 12. Detailed lists of the modified MAPT sense and antisense strand nucleotide sequences targeting mouse MAPT transcript are shown in Table 13.

It is to be understood that, throughout the application, a duplex name without a decimal is equivalent to a duplex name with a decimal which merely references the batch number of the duplex. For example, AD-523561 is equivalent to AD-523561.1.

35

In vitro screening in BE(2)-C and Neuro-2a cells

i. Cell culture and transfections:

BE(2)-C (ATCC) were transfected by adding 5µl of Opti-MEM plus 0.1µl of Lipofectamine RNAimax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well,

with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Forty μ l of 1:1 mixture of Minimum Essential Medium and F12 Medium (ThermoFisher) containing $\sim 5 \times 10^3$ cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. The results of the screening of the dsRNA agents listed in Tables 3-8 and 12-13 in BE(2)-C cells are shown in Tables 9-11 and table 14, respectively. For screen 1 shown in Table 9, four dose experiments were performed at 50nM, 10nM, 1nM and 0.1nM. For screens 2-3 shown in Tables 10-11, three dose experiments were performed at 10nM, 1nM and 0.1nM. For screen 4 shown in Table 14, two dose experiments were performed at 10nM and 0.1nM. The results of the screening of the dsRNA agents for screens 5-8 listed in Tables 16-23 in BE(2)-C cells are shown in Table 24. For screens 5-8, three dose experiments were performed at 10nM, 1nM and 0.1nM.

Neuro-2a (ATCC) were transfected by adding 5 μ l of Opti-MEM plus 0.1 μ l of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA, cat # 13778-150) to 5 μ l of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Forty μ l of Minimum Essential Medium (ThermoFisher) containing $\sim 5 \times 10^3$ cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. The results of the screening of the dsRNA agents listed in Tables 12-13 in Neuro-2a (mouse) cells are shown in Table 15. For screen 4 shown in Table 15, two dose experiments were performed at 10nM and 0.1nM.

ii. *Total RNA isolation using DYNABEADS mRNA Isolation Kit:*

RNA was isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADS (Invitrogen, cat#61012). Briefly, 70 μ l of Lysis/Binding Buffer and 10 μ l of lysis buffer containing 3 μ l of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 150 μ l Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150 μ l Elution Buffer, re-captured and supernatant removed.

iii. *cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):*

Ten μ l of a master mix containing 1 μ l 10X Buffer, 0.4 μ l 25X dNTPs, 1 μ l 10x Random primers, 0.5 μ l Reverse Transcriptase, 0.5 μ l RNase inhibitor and 6.6 μ l of H₂O per reaction was added to RNA isolated above. Plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2h 37°C.

iv. *Real time PCR:*

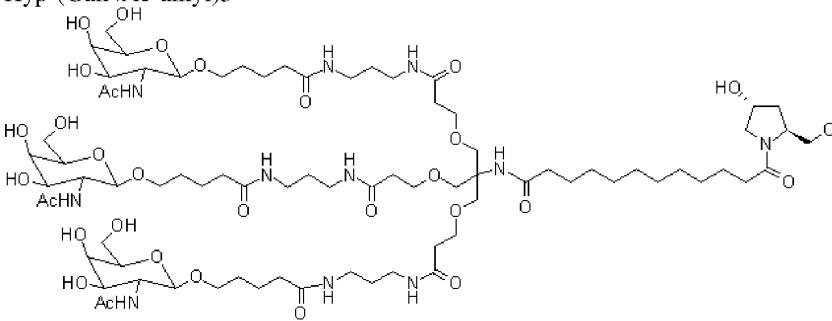
Two μ l of cDNA and 5 μ l Lightcycler 480 probe master mix (Roche Cat # 04887301001) were added to either 0.5 μ l of Human GAPDH TaqMan Probe (4326317E) and 0.5 μ l human MAPT probe (hs00902194_m1, Thermo) or 0.5 μ l Mouse GAPDH TaqMan Probe (4352339E) and 0.5 μ l mouse MAPT probe (Mm00521988_m1, Thermo) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each

duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the $\Delta\Delta C_t$ method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

- 5 **Table 2.** Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds, and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position in the parent nucleotide (i.e., it is a 2'-deoxy-2'-fluoronucleotide).

10

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3'-phosphate
Abs	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine-3'-phosphorothioate
Us	uridine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'-phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'-phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'-phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L96	<p>N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol</p> <p>Hyp-(GalNAc-alkyl)3</p> 
Y34	2-hydroxymethyl-tetrahydrofuran-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofuran-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
dT	2'-deoxythymidine-3'-phosphate
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
dUs	2'-deoxyuridine-3'-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate

Table 3. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 1

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-523799.1	AUAGUCUACAA ACCAGUUGAA	13	NM_016841.4_977-997_C21U_s	977-997	UUCAACUGGUUUG UAGACUAAUU	88	NM_016841.4_975-997_G1A_as	975-997
AD-523802.1	GUCUACAAACC AGUUGACCUA	14	NM_016841.4_980-1000_G21U_s	980-1000	UAGGUCAACUGGU UUGUAGACUA	89	NM_016841.4_978-1000_C1A_as	978-1000
AD-523795.1	GCAAAUAGUCU ACAAACCAGA	15	NM_016841.4_973-993_s	973-993	UCUGGUUUGUAGA CUAUUUGCAC	90	NM_016841.4_971-993_as	971-993
AD-523810.1	ACCAGUUGACC UGAGCAAGGA	16	NM_016841.4_988-1008_s	988-1008	UCCUUGCUCAGGU CAACUGGUUU	91	NM_016841.4_986-1008_as	986-1008
AD-523809.1	AACCAGUUGAC CUGAGCAAGA	17	NM_016841.4_987-1007_G21U_s	987-1007	UCUUGCUCAGGUC AACUGGUUUG	92	NM_016841.4_985-1007_C1A_as	985-1007
AD-1019331.1	UGCAAAUAGUC UACAAACCAA	18	NM_016841.4_972-992_G21U_s	972-992	UUGGUUUGUAGAC UAUUUGCACA	93	NM_005910.5_1237-1259_C1U_as	970-992
AD-523801.1	AGUCUACAAAC CAGUUGACCA	19	NM_016841.4_979-999_s	979-999	UGGUCAACUGGUU UGUAGACUAAU	94	NM_016841.4_977-999_as	977-999
AD-523823.1	AGCAAGGUGAC CUCCAAGUGA	20	NM_016841.4_1001-1021_s	1001-1021	UCACUUGGAGGUC ACCUUGCACA	95	NM_016841.4_999-1021_as	999-1021
AD-523798.1	AAUAGUCUACA AACCAGUUGA	21	NM_016841.4_976-996_A21U_s	976-996	UCAACUGGUUUGU AGACUAAUUUG	96	NM_016841.4_974-996_U1A_as	974-996
AD-523816.1	UGACCUGAGCA AGGUGACCUA	22	NM_016841.4_994-1014_C21U_s	994-1014	UAGGUCACCUUGC UCAGGUCAAC	97	NM_016841.4_992-1014_G1A_as	992-1014
AD-523824.1	GCAAGGUGACC UCCAAGUGUA	23	NM_016841.4_1002-1022_G21U_s	1002-1022	UACACUUGGAGGU CACCUUGCUC	98	NM_016841.4_1000-1022_C1A_as	1000-1022
AD-523800.1	UAGUCUACAAA CCAGUUGACA	24	NM_016841.4_978-998_C21U_s	978-998	UGUCAACUGGUUU GUAGACUAAU	99	NM_016841.4_976-998_G1A_as	976-998
AD-523796.1	CAAAUAGUCUA CAAACCAGUA	25	NM_016841.4_974-994_s	974-994	UACUGGUUUGUAG ACUAAUUGCA	100	NM_016841.4_972-994_as	972-994
AD-523803.1	UCUACAAACCA GUUGACCUGA	26	NM_016841.4_981-1001_A21U_s	981-1001	UCAGGUCAACUGG UUUGUAGACU	101	NM_016841.4_979-1001_U1A_as	979-1001
AD-523817.1	GACCUGAGCAA GGUGACCUCA	27	NM_016841.4_995-1015_C21U_s	995-1015	UGAGGUCACCUUG CUCAGGUCAA	102	NM_016841.4_993-1015_G1A_as	993-1015
AD-523825.1	CAAGGUGACCU CCAAGUGUGA	28	NM_016841.4_1003-1023_G21U_s	1003-1023	UCACACUUGGAGG UCACCUUGCU	103	NM_016841.4_1001-1023_C1A_as	1001-1023
AD-523811.1	CCAGUUGACCU GAGCAAGGUA	29	NM_016841.4_989-1009_G21U_s	989-1009	UACCUUGCUCAGG UCAACUGGUU	104	NM_016841.4_987-1009_C1A_as	987-1009
AD-523854.1	GGCAACAUCCA UCAUAAACCA	30	NM_016841.4_1031-1051_A21U_s	1031-1051	UGGUUUAUGAUGG AUGUUGCCUA	105	NM_016841.4_1029-1051_U1A_as	1029-1051
AD-523797.1	AAAUAGUCUAC AAACCAGUUA	31	NM_016841.4_975-995_G21U_s	975-995	UAACUGGUUUGUA GACUAAUUGC	106	NM_016841.4_973-995_C1A_as	973-995

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-523805.1	UACAAACCAGU UGACCUGAGA	32	NM_016841.4_983-1003_C21U_s	983-1003	UCUCAGGUCAACU GGUUUGUAGA	107	NM_016841.4_981-1003_G1A_as	981-1003
AD-523814.1	GUUGACCUGAG CAAGGUGACA	33	NM_016841.4_992-1012_C21U_s	992-1012	UGUCACCUUGCUC AGGUCAACUG	108	NM_016841.4_990-1012_G1A_as	990-1012
AD-523804.1	CUACAAACCAG UUGACCUGAA	34	NM_016841.4_982-1002_G21U_s	982-1002	UUCAGGUCAACUG GUUUGUAGAC	109	NM_016841.4_980-1002_C1A_as	980-1002
AD-1019356.1	GUGUGCAAAUA GUCUACAAAA	35	NM_005910.5_1236-1256_C21A_s	1236-1256	UUUUGUAGACUAU UUGCACACUG	110	NM_005910.5_1234-1256_G1U_as	1234-1256
AD-523846.1	GCUCAUUAGGC AACAUCUAUA	36	NM_016841.4_1023-1043_C21U_s	1023-1043	UAUGGAUGUUGCC UAAUGAGCCA	111	NM_016841.4_1021-1043_G1A_as	1021-1043
AD-523808.1	AAACCAGUUGA CCUGAGCAAA	37	NM_016841.4_986-1006_G21U_s	986-1006	UUUGCUCAGGUCA ACUGGUUUGU	112	NM_016841.4_984-1006_C1A_as	984-1006
AD-523835.1	CCAAGUGUGGC UCAUUAGGCA	38	NM_016841.4_1014-1034_A21U_s	1014-1034	UGCCUAAUGAGCC ACACUUGGAG	113	NM_016841.4_1012-1034_U1A_as	1012-1034
AD-1019357.1	UGUGCAAAUAG UCUACAAACA	39	NM_005910.5_1237-1257_C21A_s	1237-1257	UGUUUGUAGACUA UUUGCACACU	114	NM_005910.5_1235-1257_G1U_as	1235-1257
AD-523853.1	AGGCAACAUC AUCAUAAACA	40	NM_016841.4_1030-1050_C21U_s	1030-1050	UGUUUAUGAUGGA UGUUGCCUAA	115	NM_016841.4_1028-1050_G1A_as	1028-1050
AD-523819.1	CCUGAGCAAGG UGACCUCCAA	41	NM_016841.4_997-1017_A21U_s	997-1017	UUGGAGGUCACCU UGCUCAGGUC	116	NM_016841.4_995-1017_U1A_as	995-1017
AD-523830.1	GACCUCCAAGU GUGGCUCAUA	42	NM_016841.4_1009-1029_s	1009-1029	UAUGAGCCACACU UGGAGGUCAC	117	NM_016841.4_1007-1029_as	1007-1029
AD-523834.1	UCCAAGUGUGG CUCAUUAGGA	43	NM_016841.4_1013-1033_C21U_s	1013-1033	UCCUAAUGAGCCA CACUUGGAGG	118	NM_016841.4_1011-1033_G1A_as	1011-1033
AD-523850.1	AUUAGGCAACA UCCAUCAUAA	44	NM_016841.4_1027-1047_A21U_s	1027-1047	UUAUGAUGGAUGU UGCCUAAUGA	119	NM_016841.4_1025-1047_U1A_as	1025-1047
AD-523820.1	CUGAGCAAGGU GACCUCCAAA	45	NM_016841.4_998-1018_G21U_s	998-1018	UUUGGAGGUCACC UUGCUCAGGU	120	NM_016841.4_996-1018_C1A_as	996-1018
AD-523849.1	CAUUAGGCAAC AUCCAUCAUA	46	NM_016841.4_1026-1046_A21U_s	1026-1046	UAUGAUGGAUGUU GCCUAAUGAG	121	NM_016841.4_1024-1046_U1A_as	1024-1046
AD-523845.1	GGCUCAUUAGG CAACAUCCAA	47	NM_016841.4_1022-1042_s	1022-1042	UUGGAUGUUGCCU AAUGAGCCAC	122	NM_016841.4_1020-1042_as	1020-1042
AD-393758.3	AGUGUGCAAAU AGUCUACAAA	48	NM_001038609.2_1065-1085_G21U_s	1065-1085	UUUGUAGACUAU UGCACACUGC	123	NM_001038609.2_1063-1085_C1A_as	1063-1085
AD-523848.1	UCAUUAGGCAA CAUCCAUCAA	49	NM_016841.4_1025-1045_s	1025-1045	UUGAUGGAUGUUG CCUAAUGAGC	124	NM_016841.4_1023-1045_as	1023-1045
AD-523840.1	AGUGUGGCUCA UUAGGCAACA	50	NM_016841.4_1017-1037_A21U_s	1017-1037	UGUUGCCUAAUGA GCCACACUUG	125	NM_016841.4_1015-1037_U1A_as	1015-1037

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-523828.1	GGUGACCUCCA AGUGUGGCUA	51	NM_016841.4_1006-1026_C21U_s	1006-1026	UAGCCACACUUGG AGGUCACCUU	126	NM_016841.4_1004-1026_G1A_as	1004-1026
AD-523822.1	GAGCAAGGUGA CCUCCAAGUA	52	NM_016841.4_1000-1020_G21U_s	1000-1020	UACUUGGAGGUCA CCUUGCUCAG	127	NM_016841.4_998-1020_C1A_as	998-1020
AD-523806.1	ACAAACCAGUU GACCUGAGCA	53	NM_016841.4_984-1004_A21U_s	984-1004	UGCUCAGGUCAAC UGGUUUGUAG	128	NM_016841.4_982-1004_U1A_as	982-1004
AD-523831.1	ACCUCCAAGUG UGGCUCAUUA	54	NM_016841.4_1010-1030_A21U_s	1010-1030	UAAUGAGCCACAC UUGGAGGUCA	129	NM_016841.4_1008-1030_U1A_as	1008-1030
AD-393757.1	CAGUGUGCAAA UAGUCUACAA	55	NM_001038609.2_1064-1084_s	1064-1084	UUGUAGACUAAUU GCACACUGCC	130	NM_001038609.2_1062-1084_as	1062-1084
AD-523839.1	AAGUGUGGCUC AUUAGGCAAA	56	NM_016841.4_1016-1036_C21U_s	1016-1036	UUUGCCUAAUGAG CCACACUUGG	131	NM_016841.4_1014-1036_G1A_as	1014-1036
AD-523815.1	UUGACCUGAGC AAGGUGACCA	57	NM_016841.4_993-1013_s	993-1013	UGGUCACCUUGCU CAGGUCAACU	132	NM_016841.4_991-1013_as	991-1013
AD-523856.1	CAACAUCCAUC AUAAACCAGA	58	NM_016841.4_1033-1053_G21U_s	1033-1053	UCUGGUUUUAUGAU GGAUGUUGCC	133	NM_016841.4_1031-1053_C1A_as	1031-1053
AD-1019330.1	GUGCAAAUAGU CUACAAACCA	59	NM_016841.4_971-991_A21U_s	971-991	UGGUUUGUAGACU AUUUGCACAC	134	NM_005910.5_1236-1258_as	969-971
AD-523829.1	UGACCUCCAAG UGUGGCUCAA	60	NM_016841.4_1008-1028_s	1008-1028	UUGAGCCACACUU GGAGGUCACC	135	NM_016841.4_1006-1028_as	1006-1028
AD-523855.1	GCAACAUCCAU CAUAAACCAA	61	NM_016841.4_1032-1052_G21U_s	1032-1052	UUGGUUUUAUGAU GAUGUUGCCU	136	NM_016841.4_1030-1052_C1A_as	1030-1052
AD-523836.1	CAAGUGUGGCU CAUUAGGCAA	62	NM_016841.4_1015-1035_A21U_s	1015-1035	UUGCCUAAUGAGC CACACUUGGA	137	NM_016841.4_1013-1035_U1A_as	1013-1035
AD-1019329.1	GCAGUGUGCAA AUAGUCUACA	63	NM_001038609.2_1063-1083_s	1063-1083	UGUAGACUAAUUG CACACUGCCG	138	NM_005910.5_1231-1253_as	1061-1083
AD-523843.1	GUGGCUCAUUA GGCAACAUA	64	NM_016841.4_1020-1040_C21U_s	1020-1040	UGAUGUUGCCUAA UGAGCCACAC	139	NM_016841.4_1018-1040_G1A_as	1018-1040
AD-523807.1	CAAACCAGUUG ACCUGAGCAA	65	NM_016841.4_985-1005_A21U_s	985-1005	UUGCUCAGGUCAA CUGGUUUGUA	140	NM_016841.4_983-1005_U1A_as	983-1005
AD-523821.1	UGAGCAAGGUG ACCUCCAAGA	66	NM_016841.4_999-1019_s	999-1019	UCUUGGAGGUCAC CUUGCUCAGG	141	NM_016841.4_997-1019_as	997-1019
AD-523826.1	AAGGUGACCUC CAAGUGUGGA	67	NM_016841.4_1004-1024_C21U_s	1004-1024	UCCACACUUGGAG GUCACCUUGC	142	NM_016841.4_1002-1024_G1A_as	1002-1024
AD-523847.1	CUCAUUAGGCA ACAUCCAUA	68	NM_016841.4_1024-1044_A21U_s	1024-1044	UGAUGGAUGUUGC CUAAUGAGCC	143	NM_016841.4_1022-1044_U1A_as	1022-1044
AD-523786.1	GUGACCUCCAA GUGUGGCUCA	69	NM_001038609.2_1104-1124_G21U_s	1104-1124	UGAGCCACACUUG GAGGUCACCU	144	NM_016841.4_1005-1027_U1A_as	1102-1124

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-523812.1	CAGUUGACCUG AGCAAGGUGA	70	NM_016841.4_990-1010_A21U_s	990-1010	UCACCUUGCUCAG GUCAACUGGU	145	NM_016841.4_988-1010_U1A_as	988-1010
AD-523827.1	AGGUGACCUCC AAGUGUGGCA	71	NM_016841.4_1005-1025_s	1005-1025	UGCCACACUUGGA GGUCACCUUG	146	NM_016841.4_1003-1025_as	1003-1025
AD-523844.1	UGGCUCAUUAG GCAACAUCCA	72	NM_016841.4_1021-1041_A21U_s	1021-1041	UGGAUGUUGCCUA AUGAGCCACA	147	NM_016841.4_1019-1041_U1A_as	1019-1041
AD-523851.1	UUAGGCAACA CCAUCAUAAA	73	NM_016841.4_1028-1048_A21U_s	1028-1048	UUUAUGAUGGAUG UUGCCUAAUG	148	NM_016841.4_1026-1048_U1A_as	1026-1048
AD-523818.1	ACCUGAGCAAG GUGACCUCCA	74	NM_016841.4_996-1016_A21U_s	996-1016	UGGAGGUCACCUU GCUCAGGUCA	149	NM_016841.4_994-1016_U1A_as	994-1016
AD-523832.1	CCUCCAAGUGU GGCUCAUUA	75	NM_016841.4_1011-1031_G21U_s	1011-1031	UUA AUGAGCCACA CUUGGAGGUC	150	NM_016841.4_1009-1031_C1A_as	1009-1031
AD-523813.1	AGUUGACCUGA GCAAGGUGAA	76	NM_016841.4_991-1011_C21U_s	991-1011	UUCACCUUGCUCU GGUCAACUGG	151	NM_016841.4_989-1011_G1A_as	989-1011
AD-523841.1	GUGUGGCUCAU UAGGCAACAA	77	NM_016841.4_1018-1038_s	1018-1038	UUGUUGCCUAAUG AGCCACACUU	152	NM_016841.4_1016-1038_as	1016-1038
AD-1019352.1	AGGCGGCAGUG UGCAAAUAGA	78	NM_005910.5_1228-1248_U21A_s	1228-1248	UCUAAUUGCACAC UGCCGCCUCC	153	NM_005910.5_1226-1248_A1U_as	1226-1248
AD-1019354.1	GCGGCAGUGUG CAAAUAGUCA	79	NM_005910.5_1230-1250_U21A_s	1230-1250	UGACUAAUUGCAC ACUGCCGCCU	154	NM_005910.5_1228-1250_A1U_as	1228-1250
AD-523852.1	UAGGCAACAUC CAUCAUAAA	80	NM_016841.4_1029-1049_C21U_s	1029-1049	UUUAUGAUGGAU GUUGCCUAAU	155	NM_016841.4_1027-1049_G1A_as	1027-1049
AD-523842.1	UGUGGCUCAUU AGGCAACAUA	81	NM_016841.4_1019-1039_C21U_s	1019-1039	UAUGUUGCCUAAU GAGCCACACU	156	NM_016841.4_1017-1039_G1A_as	1017-1039
AD-523833.1	CUCCAAGUGUG GCUCAUUAGA	82	NM_016841.4_1012-1032_G21U_s	1012-1032	UCUAAUGAGCCAC ACUUGGAGGU	157	NM_016841.4_1010-1032_C1A_as	1010-1032
AD-1019328.1	GGCAGUGUGCA AAUAGUCUAA	83	NM_00103860_9.2_1062-1082_C21U_s	1062-1082	UUAGACUAAUUGC ACACUGCCGC	158	NM_005910.5_1230-1252_G1U_as	1060-1082
AD-1019355.1	CGGCAGUGUGC AAAUAGUCUA	84	NM_005910.5_1231-1251_s	1231-1251	UAGACUAAUUGCA CACUGCCGCC	159	NM_005910.5_1229-1251_as	1229-1251
AD-1019353.1	GGCGGCAGUGU GCAAAUAGUA	85	NM_005910.5_1229-1249_C21A_s	1229-1249	UACUAAUUGCACA CUGCCGCCUC	160	NM_005910.5_1227-1249_G1U_as	1227-1249
AD-1019350.1	GGAGGCGGCAG UGUGCAAAUA	86	NM_005910.5_1226-1246_s	1226-1246	UAUUUGCACACUG CCGCCUCCCG	161	NM_005910.5_1224-1246_as	1224-1246
AD-1019351.1	GAGGCGGCAGU GUGCAAAUAA	87	NM_005910.5_1227-1247_G21A_s	1227-1247	UUAUUUGCACACU GCCGCCUCCC	162	NM_005910.5_1225-1247_C1U_as	1225-1247

Table 4. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 2

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-535094.1	AGCUCGCAU GGUCAGUA AAAA	388	NM_016841.4_5 20-540_G21U_s	520-540	UUUUUACUGAC CAUGCGAGCUU G	476	NM_016841.4_5 18-540_C1A_as	518-540
AD-535095.1	GCUCGCAUG GUCAGUAA AAGA	389	NM_016841.4_5 21-541_C21U_s	521-541	UCUUUUACUGA CCAUGCGAGCUU	477	NM_016841.4_5 19-541_G1A_as	519-541
AD-538647.1	UAUUGUGU GUUUUAAC AAUA	390	NM_016841.4_5 464- 5484_G21U_s	5464- 5484	UAUUUGTUA ACACACAAUACA	478	NM_016841.4_5 462- 5484_C1A_as	5462- 5484
AD-535922.1	CAGCAACAA AGGAUUUG AAAA	391	NM_016841.4_1 813- 1833_C21U_s	1813- 1833	UUUUCAAAUCC UUUGUUGCUGC C	479	NM_016841.4_1 811- 1833_G1A_as	1811- 1833
AD-536317.1	GCUAACCAG UUCUCUUUG UAA	392	NM_016841.4_2 378- 2398_A21U_s	2378- 2398	UUACAAAGAGA ACUGGUUAGCCC	480	NM_016841.4_2 376- 2398_U1A_as	2376- 2398
AD-536911.1	UAGUUGGA UUUGUCUG UUUAA	393	NM_016841.4_3 242-3262_s	3242- 3262	UUAACAGACA AAUCCAACUACA	481	NM_016841.4_3 240-3262_as	3240- 3262
AD-538626.1	GUCUGUGA AUGUCUUA AUAGA	394	NM_016841.4_5 442-5462_s	5442- 5462	UCUAUATAGACA UUCACAGACAG	482	NM_016841.4_5 440-5462_as	5440- 5462
AD-535864.1	CAGGCAAUU CCUUUUGAU UCA	395	NM_016841.4_1 665-1685_s	1665- 1685	UGAAUCAAAG GAAUUGCCUGA G	483	NM_016841.4_1 663-1685_as	1663- 1685
AD-535925.1	CAACAAAGG AUUUGAAA CUUA	396	NM_016841.4_1 816- 1836_G21U_s	1816- 1836	UAAGUUTCAAAU CCUUUGUUGCU	484	NM_016841.4_1 814- 1836_C1A_as	1814- 1836
AD-538012.1	GCUGACUCA CUUUAUCAA UAA	397	NM_016841.4_4 667- 4687_G21U_s	4667- 4687	UUAUUGAUAAA GUGAGUCAGCA G	485	NM_016841.4_4 665- 4687_C1A_as	4665- 4687
AD-536872.1	GCAGCUGAA CAUAUACAU AGA	398	NM_016841.4_3 183- 3203_A21U_s	3183- 3203	UCUAUGTAUAUG UUCAGCUGCUC	486	NM_016841.4_3 181- 3203_U1A_as	3181- 3203
AD-536954.1	AGGACGCAU GUAUCUUG AAAA	399	NM_001038609. 2_3422-3442_s	3422- 3442	UUUUCAAGAU CAUGCGUCCUUU	487	NM_016841.4_3 314-3336_as	3420- 3442
AD-536964.1	UAUCUUGA AAUGCUUG UAAAA	400	NM_016841.4_3 326- 3346_G21U_s	3326- 3346	UUUUACAAGCA UUUCAAGAUAC A	488	NM_016841.4_3 324- 3346_C1A_as	3324- 3346
AD-536318.1	CUAACAGU UCUCUUUGU AAA	401	NM_016841.4_2 379- 2399_G21U_s	2379- 2399	UUUACAAAGAG AACUGGUUAGC C	489	NM_016841.4_2 377- 2399_C1A_as	2377- 2399
AD-536976.1	CUUGUAAA GAGGUUUC UAACA	402	NM_016841.4_3 338- 3358_C21U_s	3338- 3358	UGUUAGAAACC UCUUUACAAGC A	490	NM_016841.4_3 336- 3358_G1A_as	3336- 3358
AD-538630.1	GUGAAUGU CUAUUAG UGUAA	403	NM_016841.4_5 446-5466_s	5446- 5466	UUACACTAUUA GACAUUCACAG	491	NM_016841.4_5 444-5466_as	5444- 5466
AD-538624.1	CUGUCUGUG AAUGUCUA UAUA	404	NM_016841.4_5 440- 5460_A21U_s	5440- 5460	UAUAUAGACAU UCACAGACAGA A	492	NM_016841.4_5 438- 5460_U1A_as	5438- 5460
AD-538594.1	AGGGACAU GAAAUCAUC UUAA	405	NM_016841.4_5 410- 5430_G21U_s	5410- 5430	UUAAGATGAUU UCAUGUCCCUCC	493	NM_016841.4_5 408- 5430_C1A_as	5408- 5430

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-536915.1	UGGAUUUG UCUGUUUA UGCUA	406	NM_016841.4_3 246-3266_s	3246-3266	UAGCAUAAACA GACAAAUCCAAC	494	NM_016841.4_3 244-3266_as	3244-3266
AD-536870.1	GAGCAGCUG AACAUUAUAC AUA	407	NM_016841.4_3 181-3201_A21U_s	3181-3201	UAUGUATAUGU UCAGCUGCUCCA	495	NM_016841.4_3 179-3201_U1A_as	3179-3201
AD-536236.1	ACAGAAACC CUGUUUUA UUGA	408	NM_016841.4_2 297-2317_A21U_s	2297-2317	UCAAUAAAACA GGGUUUCUGUG G	496	NM_016841.4_2 295-2317_U1A_as	2295-2317
AD-536319.1	UAACCAGUU CUCUUUGUA AGA	409	NM_016841.4_2 380-2400_G21U_s	2380-2400	UCUUACAAAGA GAACUGGUUAG C	497	NM_016841.4_2 378-2400_C1A_as	2378-2400
AD-536966.1	UCUUGAAA UGCUUGUA AAGAA	410	NM_016841.4_3 328-3348_G21U_s	3328-3348	UUCUUUACAAG CAUUUCAAGAU A	498	NM_016841.4_3 326-3348_C1A_as	3326-3348
AD-538643.1	AGUGUAUU GUGUGUUU UAACA	411	NM_016841.4_5 460-5480_A21U_s	5460-5480	UGUUAACACAC ACAAUACACUA U	499	NM_016841.4_5 458-5480_U1A_as	5458-5480
AD-536873.1	CAGCUGAAC AUUAUCAU AGAA	412	NM_016841.4_3 184-3204_s	3184-3204	UUCUAUGUAUA UGUUCAGCUGC U	500	NM_016841.4_3 182-3204_as	3182-3204
AD-536952.1	AAAGGACGC AUGUAUCU UGAA	413	NM_001038609. 2_3420-3440_s	3420-3440	UUCAAGAUACA UGCGUCCUUUU U	501	NM_016841.4_3 312-3334_U1A_as	3418-3440
AD-536959.1	GCAUGUAUC UUGAAUG CUUA	414	NM_016841.4_3 321-3341_G21U_s	3321-3341	UAAGCATUUCAA GAUACAUGCGU	502	NM_016841.4_3 319-3341_C1A_as	3319-3341
AD-537921.1	ACGCUGGCU UGUGAUCU UAAA	415	NM_016841.4_4 529-4549_A21U_s	4529-4549	UUUAAGAUCAC AAGCCAGCGUGC	503	NM_016841.4_4 527-4549_U1A_as	4527-4549
AD-538652.1	UUUUAACA AAUGAUUU ACACA	416	NM_016841.4_5 473-5493_s	5473-5493	UGUGUAAAUCA UUUGUAAAAAC A	504	NM_016841.4_5 471-5493_as	5471-5493
AD-538649.1	UUGUGUGU UUUAACAA AUGAA	417	NM_016841.4_5 466-5486_s	5466-5486	UUCAUUTGUUAA AACACACAAUA	505	NM_016841.4_5 464-5486_as	5464-5486
AD-538623.1	UCUGUCUGU GAAUGUCU AUAA	418	NM_016841.4_5 439-5459_s	5439-5459	UUAUAGACAUU CACAGACAGAA A	506	NM_016841.4_5 437-5459_as	5437-5459
AD-538573.1	GCAAGUCCC AUGAUUUC UUCA	419	NM_016841.4_5 369-5389_G21U_s	5369-5389	UGAAGAAAUCA UGGGACUUGCA A	507	NM_016841.4_5 367-5389_C1A_as	5367-5389
AD-537920.1	CACGCUGGC UUGUGAUC UUAA	420	NM_016841.4_4 528-4548_A21U_s	4528-4548	UUAAGATCACAA GCCAGCGUGCC	508	NM_016841.4_4 526-4548_U1A_as	4526-4548
AD-536939.1	UUCACCAGA GUGACUAU GAUA	421	NM_001038609. 2_3338-3358_s	3338-3358	UAUCAUAGUCA CUCUGGUGAAU C	509	NM_016841.4_3 268-3290_U1A_as	3336-3358
AD-538015.1	GACUCACUU UAUCAUA GUUA	422	NM_016841.4_4 670-4690_C21U_s	4670-4690	UAACUATUGAUA AAGUGAGUCAG	510	NM_016841.4_4 668-4690_G1A_as	4668-4690
AD-536953.1	AAGGACGCA UGUAUCUU GAAA	423	NM_001038609. 2_3421-3441_s	3421-3441	UUUCAAGAUAC AUGCGUCCUUU U	511	NM_016841.4_3 313-3335_U1A_as	3419-3441

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-536237.1	CAGAAACCC UGUUUUUAU UGAA	424	NM_016841.4_2 298- 2318_G21U_s	2298- 2318	UUCAAUAAAAC AGGGUUUCUGU G	512	NM_016841.4_2 296- 2318_C1A_as	2296- 2318
AD-538628.1	CUGUGAAU GUCUAUAU AGUGA	425	NM_016841.4_5 444-5464_s	5444- 5464	UCACUATAUAGA CAUUCACAGAC	513	NM_016841.4_5 442-5464_as	5442- 5464
AD-538632.1	GAAUGUCU AUUAUAGUG UAUUA	426	NM_016841.4_5 448- 5468_G21U_s	5448- 5468	UAAUACACUAU AUAGACAUUCA C	514	NM_016841.4_5 446- 5468_C1A_as	5446- 5468
AD-536975.1	GCUUGUAA AGAGGUUU CUAAA	427	NM_016841.4_3 337- 3357_C21U_s	3337- 3357	UUUAGAAACCU CUUUACAAGCA U	515	NM_016841.4_3 335- 3357_G1A_as	3335- 3357
AD-538599.1	CAUGAAAUC AUCUUAGCU UAA	428	NM_016841.4_5 415- 5435_G21U_s	5415- 5435	UUAAGCTAAGAU GAUUUCAUGUC	516	NM_016841.4_5 413- 5435_C1A_as	5413- 5435
AD-536978.1	UGUAAAAGA GGUUUCUA ACCCA	429	NM_016841.4_3 340- 3360_A21U_s	3340- 3360	UGGGUUAGAAA CCUCUUUACAAG	517	NM_016841.4_3 338- 3360_U1A_as	3338- 3360
AD-536956.1	GACGCAUGU AUCUUGAA AUGA	430	NM_016841.4_3 318- 3338_C21U_s	3318- 3338	UCAUUUCAAGA UACAUGCUGCCU	518	NM_016841.4_3 316- 3338_G1A_as	3316- 3338
AD-538571.1	UUGCAAGUC CCAUGAUUU CUA	431	NM_001038609. 2_5207-5227_s	5207- 5227	UAGAAATCAUGG GACUUGCAAGU	519	NM_016841.4_5 365-5387_as	5205- 5227
AD-535921.1	GCAGCAACA AAGGAUUU GAAA	432	NM_016841.4_1 812- 1832_A21U_s	1812- 1832	UUUCAAUCCU UUGUUGCUGCC A	520	NM_016841.4_1 810- 1832_U1A_as	1810- 1832
AD-538593.1	GAGGGACA UGAAAUCA UCUUA	433	NM_016841.4_5 409- 5429_A21U_s	5409- 5429	UAAGAUGAUUU CAUGUCCCUCCC	521	NM_016841.4_5 407- 5429_U1A_as	5407- 5429
AD-537974.1	GCUAGAUA GGAUUAUC UGUAA	434	NM_016841.4_4 629-4649_s	4629- 4649	UUACAGTAUAUC CUAUCUAGCCC	522	NM_016841.4_4 627-4649_as	4627- 4649
AD-537973.1	GGCUAGAU AGGAUAUA CUGUA	435	NM_016841.4_4 628- 4648_A21U_s	4628- 4648	UACAGUAUAUC CUAUCUAGCCCA	523	NM_016841.4_4 626- 4648_U1A_as	4626- 4648
AD-536982.1	AAGAGGUU UCUAACCCA CCCA	436	NM_016841.4_3 344-3364_s	3344- 3364	UGGGUGGGUUA GAAACCUCUUU A	524	NM_016841.4_3 342-3364_as	3342- 3364
AD-535918.1	GUGGCAGCA ACAAAGGA UUUA	437	NM_016841.4_1 809- 1829_G21U_s	1809- 1829	UAAAUCCUUUG UUGCUGCCACUG	525	NM_016841.4_1 807- 1829_C1A_as	1807- 1829
AD-538627.1	UCUGUGAA UGUCUAUA UAGUA	438	NM_016841.4_5 443- 5463_G21U_s	5443- 5463	UACUAUAUAGA CAUUCACAGACA	526	NM_016841.4_5 441- 5463_C1A_as	5441- 5463
AD-536913.1	GUUGGAUU UGUCUGUU UAUGA	439	NM_016841.4_3 244- 3264_C21U_s	3244- 3264	UCAUAAACAGA CAAUCCAACUA	527	NM_016841.4_3 242- 3264_G1A_as	3242- 3264
AD-536869.1	GGAGCAGCU GAACAUUA ACAA	440	NM_016841.4_3 180-3200_s	3180- 3200	UUGUAUAUGUU CAGCUGCUCCAG	528	NM_016841.4_3 178-3200_as	3178- 3200
AD-536965.1	AUCUUGAA AUGCUUGU AAAGA	441	NM_016841.4_3 327- 3347_A21U_s	3327- 3347	UCUUUACAAGC AUUUCAAGAU C	529	NM_016841.4_3 325- 3347_U1A_as	3325- 3347

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-537914.1	AAAAGGCAC GCUGGCUUG UGA	442	NM_016841.4_4 522- 4542_A21U_s	4522- 4542	UCACAAGCCAGC GUGCCUUUUA	530	NM_016841.4_4 520- 4542_U1A_as	4520- 4542
AD-536504.1	CCAUACUGA GGGUGAAA UAAA	443	NM_016841.4_2 667- 2687_A21U_s	2667- 2687	UUAUUUTCACCC UCAGUAUGGAG	531	NM_016841.4_2 665- 2687_U1A_as	2665- 2687
AD-538013.1	CUGACUCAC UUUAUCAA UAGA	444	NM_016841.4_4 668-4688_s	4668- 4688	UCUAUUGAUAA AGUGAGUCAGC A	532	NM_016841.4_4 666-4688_as	4666- 4688
AD-537579.1	UUCUGGUU UGGGUACA GUUAA	445	NM_016841.4_4 083- 4103_A21U_s	4083- 4103	UUAACUGUACCC AAACCAGAAGU	533	NM_016841.4_4 081- 4103_U1A_as	4081- 4103
AD-538629.1	UGUGAAUG UCUAUAUA GUGUA	446	NM_016841.4_5 445- 5465_A21U_s	5445- 5465	UACACUAUAUA GACAUUCACAG A	534	NM_016841.4_5 443- 5465_U1A_as	5443- 5465
AD-536233.1	UCCACAGAA ACCCUGUUU UAA	447	NM_016841.4_2 294-2314_s	2294- 2314	UUAAAACAGGG UUUCUGUGGAG C	535	NM_016841.4_2 292-2314_as	2292- 2314
AD-538141.1	GAUUUCAAC CACAUUUGC UAA	448	NM_016841.4_4 842- 4862_G21U_s	4842- 4862	UUAGCAAAUGU GGUUGAAAUCA U	536	NM_016841.4_4 840- 4862_C1A_as	4840- 4862
AD-538622.1	UUCUGUCUG UGAAUGUC UAUA	449	NM_016841.4_5 438- 5458_A21U_s	5438- 5458	UAUAGACAUUC ACAGACAGAAA G	537	NM_016841.4_5 436- 5458_U1A_as	5436- 5458
AD-537580.1	UCUGGUUU GGGUACAG UAAAA	450	NM_016841.4_4 084- 4104_A21U_s	4084- 4104	UUUAACTGUACC CAAACCAGAAG	538	NM_016841.4_4 082- 4104_U1A_as	4082- 4104
AD-536505.1	CAUACUGAG GGUGAAAU UAAA	451	NM_016841.4_2 668- 2688_G21U_s	2668- 2688	UUUAAUTUCACC CUCAGUAUGGA	539	NM_016841.4_2 666- 2688_C1A_as	2666- 2688
AD-537918.1	GGCACGCUG GCUUGUGA UCUA	452	NM_016841.4_4 526-4546_s	4526- 4546	UAGAUCACAAG CCAGCGUGCCUU	540	NM_016841.4_4 524-4546_as	4524- 4546
AD-537913.1	GAAAAGGC ACGCUGGCU UGUA	453	NM_016841.4_4 521- 4541_G21U_s	4521- 4541	UACAAGCCAGCG UGCCUUUCAA	541	NM_016841.4_4 519- 4541_C1A_as	4519- 4541
AD-538642.1	UAGUGUAU UGUGUGUU UAAAA	454	NM_016841.4_5 459- 5479_C21U_s	5459- 5479	UUUAAAACACA CAAUACACUAU A	542	NM_016841.4_5 457- 5479_G1A_as	5457- 5479
AD-536877.1	UGAACUAU UACAUAGA UGUUA	455	NM_016841.4_3 188- 3208_G21U_s	3188- 3208	UAACAUCUAUG UAUAUGUUCAG C	543	NM_016841.4_3 186- 3208_C1A_as	3186- 3208
AD-538650.1	UGUGUGUU UUAACAAA UGAUA	456	NM_016841.4_5 467-5487_s	5467- 5487	UAUCAUTUGUUA AAACACACAAU	544	NM_016841.4_5 465-5487_as	5465- 5487
AD-538625.1	UGUCUGUG AAUGUCUA UAUAA	457	NM_016841.4_5 441- 5461_G21U_s	5441- 5461	UUAUAUAGACA UUCACAGACAG A	545	NM_016841.4_5 439- 5461_C1A_as	5439- 5461
AD-537911.1	UUGAAAAG GCACGCUGG CUUA	458	NM_016841.4_4 519- 4539_G21U_s	4519- 4539	UAAGCCAGCGU GCCUUUCAAU U	546	NM_016841.4_4 517- 4539_C1A_as	4517- 4539
AD-538014.1	UGACUCACU UUAUCAAU AGUA	459	NM_016841.4_4 669-4689_s	4669- 4689	UACUAUTGAUAA AGUGAGUCAGC	547	NM_016841.4_4 667-4689_as	4667- 4689

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-538634.1	AUGUCUAU AUAGUGUA UUGUA	460	NM_016841.4_5 450- 5470_G21U_s	5450- 5470	UACAAUACACU AUAUAGACAUU C	548	NM_016841.4_5 448- 5470_C1A_as	5448- 5470
AD-536979.1	GUAAAGAG GUUUCUAAAC CCAA	461	NM_016841.4_3 341- 3361_C21U_s	3341- 3361	UUGGGUTAGAA ACCUCUUUACAA	549	NM_016841.4_3 339- 3361_G1A_as	3339- 3361
AD-538641.1	AUAGUGUA UUGUGUGU UUUAA	462	NM_016841.4_5 458- 5478_A21U_s	5458- 5478	UAAAAACACAC AAUACACUAUA U	550	NM_016841.4_5 456- 5478_U1A_as	5456- 5478
AD-537912.1	UGAAAAGG CACGCUGGC UUGA	463	NM_016841.4_4 520-4540_s	4520- 4540	UCAAGCCAGCGU GCCUUUUCAAU	551	NM_016841.4_4 518-4540_as	4518- 4540
AD-537761.1	CUCAUUACU GCCAACAGU UUA	464	NM_016841.4_4 329- 4349_C21U_s	4329- 4349	UAAACUGUUGG CAGUAAUGAGG G	552	NM_016841.4_4 327- 4349_G1A_as	4327- 4349
AD-537917.1	AGGCACGCU GGCUUGUG AUCA	465	NM_016841.4_4 525-4545_s	4525- 4545	UGAUCACAAGCC AGCGUGCCUUU	553	NM_016841.4_4 523-4545_as	4523- 4545
AD-537916.1	AAGGCACGC UGGCUUGU GAUA	466	NM_016841.4_4 524- 4544_C21U_s	4524- 4544	UAUCACAAGCCA GCGUGCCUUU	554	NM_016841.4_4 522- 4544_G1A_as	4522- 4544
AD-538432.1	GAUACCUG CGUGUCCCA UCA	467	NM_016841.4_5 208-5228_s	5208- 5228	UGAUGGGACAC GCAGGUGAUCA C	555	NM_016841.4_5 206-5228_as	5206- 5228
AD-538529.1	CUCACCUCC UAAUAGAC UUAA	468	NM_016841.4_5 305- 5325_G21U_s	5305- 5325	UUAAGUCUAUU AGGAGGUGAGG C	556	NM_016841.4_5 303- 5325_C1A_as	5303- 5325
AD-537867.1	CAGCCUAAG AUCAUGGU UUAA	469	NM_016841.4_4 475- 4495_G21U_s	4475- 4495	UUAACCAUGA UCUUAGGCUGG C	557	NM_016841.4_4 473- 4495_C1A_as	4473- 4495
AD-536503.1	UCCAUAACUG AGGGUGAA AUUA	470	NM_016841.4_2 666- 2686_A21U_s	2666- 2686	UAAUUUCACCCU CAGUAUGGAGU	558	NM_016841.4_2 664- 2686_U1A_as	2664- 2686
AD-537582.1	UGGUUUGG GUACAGUU AAAGA	471	NM_016841.4_4 086- 4106_G21U_s	4086- 4106	UCUUUACUGU ACCCAAACCAGA	559	NM_016841.4_4 084- 4106_C1A_as	4084- 4106
AD-537915.1	AAAGGCACG CUGGCUUGU GAA	472	NM_016841.4_4 523-4543_s	4523- 4543	UUCACAAGCCAG CGUGCCUUUUC	560	NM_016841.4_4 521-4543_as	4521- 4543
AD-537919.1	GCACGCUGG CUUGUGAUC UUA	473	NM_016841.4_4 527- 4547_A21U_s	4527- 4547	UAAGAUCACAA GCCAGCGUGCCU	561	NM_016841.4_4 525- 4547_U1A_as	4525- 4547
AD-537581.1	CUGGUUUG GGUACAGU UAAAA	474	NM_016841.4_4 085- 4105_G21U_s	4085- 4105	UUUUUACUGUA CCCAAACCAGAA	562	NM_016841.4_4 083- 4105_C1A_as	4083- 4105
AD-538483.1	UUCUCUUCA GCUUUGAA AAGA	475	NM_016841.4_5 259- 5279_G21U_s	5259- 5279	UCUUUCAAAG CUGAAGAGAAA U	563	NM_016841.4_5 257- 5279_C1A_as	5257- 5279

Table 5. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 3

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-523561.1	AGCUCGCAUGGUCAGUAAAAA	828	NM_016841.4_520-540_G21U_s	520-540	UUUUUACUGACC AUGCGAGCUUG	921	NM_016841.4_518-540_C1A_as	518-540
AD-523565.1	CGCAUGGUCAGUAAAAAGCAAA	829	NM_016841.4_524-544_A21U_s	524-544	UUUGCUUUUACUGACCAUGCGAG	922	NM_016841.4_522-544_U1A_as	522-544
AD-523562.1	GCUCGCAUGGU CAGUAAAAGA	830	NM_016841.4_521-541_C21U_s	521-541	UCUUUUACUGAC CAUGCGAGCUU	923	NM_016841.4_519-541_G1A_as	519-541
AD-526914.1	UUGCAAGUCCCAUGAUUUCUA	831	NM_001038609.2_5207-5227_s	5207-5227	UAGAAAUCAUGG GACUUGCAAGU	924	NM_016841.4_536-5-5387_as	5205-5227
AD-526394.1	GACUCACUUUA UCAAUAGUUA	832	NM_016841.4_4670-4690_C21U_s	4670-4690	UAACUAUUGAUA AAGUGAGUCAG	925	NM_016841.4_466-8-4690_G1A_as	4668-4690
AD-395452.1	AAAGGACGCAU GUAUCUUGAA	833	NM_001038609.2_3420-3440_s	3420-3440	UUCAAGAUACAU GCGUCCUUUUU	926	NM_001038609.2_3418-3440_as	3418-3440
AD-525343.1	UCUUGAAAUGC UUGUAAAAGAA	834	NM_016841.4_3328-3348_G21U_s	3328-3348	UUCUUUACAAGC AUUUCAAGUA	927	NM_016841.4_332-6-3348_C1A_as	3326-3348
AD-524274.1	CAGGCAAUUC UUUUGAUUCA	835	NM_016841.4_1665-1685_s	1665-1685	UGAAUCAAAAGG AAUUGCCUGAG	928	NM_016841.4_166-3-1685_as	1663-1685
AD-526956.1	GAGGGACAUGA AAUCAUCUUA	836	NM_016841.4_5409-5429_A21U_s	5409-5429	UAAGAUGAUUUC AUGUCCCUCCC	929	NM_016841.4_540-7-5429_U1A_as	5407-5429
AD-526986.1	UCUGUCUGUGA AUGUCUAUAA	837	NM_016841.4_5439-5459_s	5439-5459	UUAUAGACAUUC ACAGACAGAAA	930	NM_016841.4_543-7-5459_as	5437-5459
AD-526296.1	GCACGUGGCU UGUGAUCUUA	838	NM_016841.4_4527-4547_A21U_s	4527-4547	UAAGAUCACAAG CCAGCGUGCCU	931	NM_016841.4_452-5-4547_U1A_as	4525-4547
AD-526988.1	UGUCUGUGAAU GUCUAUAUAA	839	NM_016841.4_5441-5461_G21U_s	5441-5461	UUAUAUAGACAU UCACAGACAGA	932	NM_016841.4_543-9-5461_C1A_as	5439-5461
AD-526957.1	AGGGACAUGAA AUCAUCUUA	840	NM_016841.4_5410-5430_G21U_s	5410-5430	UUAAGAUGAUUU CAUGUCCCUCC	933	NM_016841.4_540-8-5430_C1A_as	5408-5430
AD-526993.1	GUGAAUGUCUA UAUAGUGUAA	841	NM_016841.4_5446-5466_s	5446-5466	UUACACUAUAUA GACAUUCACAG	934	NM_016841.4_544-4-5466_as	5444-5466
AD-527013.1	UGUGUGUUUUA ACAAAUGAUA	842	NM_016841.4_5467-5487_s	5467-5487	UAUCAUUUGUUA AAACACACAAU	935	NM_016841.4_546-5-5487_as	5465-5487
AD-526936.1	GCAAGUCCCAU GAUUUCUUCA	843	NM_016841.4_5369-5389_G21U_s	5369-5389	UGAAGAAAUCAU GGGACUUGCAA	936	NM_016841.4_536-7-5389_C1A_as	5367-5389
AD-395453.1	AAGGACGCAUG UAUCUUGAAA	844	NM_001038609.2_3421-3441_s	3421-3441	UUUCAAGAUACA UGCGUCCUUUU	937	NM_001038609.2_3419-3441_as	3419-3441
AD-526989.1	GUCUGUGAAUG UCUAUUAUAGA	845	NM_016841.4_5442-5462_s	5442-5462	UCUAUAUAGACA UUCACAGACAG	938	NM_016841.4_544-0-5462_as	5440-5462
AD-524719.1	CUAACCAGUUC UCUUUGUAAA	846	NM_016841.4_2379-2399_G21U_s	2379-2399	UUUACAAAGAGA ACUGGUUAGCC	939	NM_016841.4_237-7-2399_C1A_as	2377-2399
AD-526423.1	GACUGUAUCCU GUUUGCUAUA	847	NM_016841.4_4715-4735_s	4715-4735	UAUAGCAAACAG GAUACAGUCUC	940	NM_016841.4_471-3-4735_as	4713-4735
AD-527010.1	UAUUGUGUGUU UUAACAAUA	848	NM_016841.4_5464-5484_G21U_s	5464-5484	UAUUUGUUAAAA CACACAAUACA	941	NM_016841.4_546-2-5484_C1A_as	5462-5484

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-525305.1	GUUGGAUUUGU CUGUUUAUGA	849	NM_016841.4_3244-3264_C21U_s	3244-3264	UCAUAAACAGAC AAAUCCAACUA	942	NM_016841.4_3242-3264_G1A_as	3242-3264
AD-526987.1	CUGUCUGUGAA UGUCUAUAUA	850	NM_016841.4_5440-5460_A21U_s	5440-5460	UAUAUAGACAUU CACAGACAGAA	943	NM_016841.4_5438-5460_U1A_as	5438-5460
AD-524331.1	GCAGCAACAAA GGAUUUGAAA	851	NM_016841.4_1812-1832_A21U_s	1812-1832	UUUCAAUCCUU UGUUGCUGCCA	944	NM_016841.4_1810-1832_U1A_as	1810-1832
AD-525266.1	GAGCAGCUGAA CAUAUACAUA	852	NM_016841.4_3181-3201_A21U_s	3181-3201	UAUGUAUAUGUU CAGCUGCUCCA	945	NM_016841.4_3179-3201_U1A_as	3179-3201
AD-525342.1	AUCUUGAAAUG CUUGUAAAGA	853	NM_016841.4_3327-3347_A21U_s	3327-3347	UCUUUACAAGCA UUUCAAGAUAC	946	NM_016841.4_3325-3347_U1A_as	3325-3347
AD-526995.1	GAAUGUCUAUA UAGUGUAUUA	854	NM_016841.4_5448-5468_G21U_s	5448-5468	UAAUACACUAUA UAGACAUUCAC	947	NM_016841.4_5446-5468_C1A_as	5446-5468
AD-526298.1	ACGCGUGGCUUG UGAUCUUAUA	855	NM_016841.4_4529-4549_A21U_s	4529-4549	UUUAAAGAUCACA AGCCAGCGUGC	948	NM_016841.4_4527-4549_U1A_as	4527-4549
AD-524718.1	GCUAACCAGUU CUCUUUGUAA	856	NM_016841.4_2378-2398_A21U_s	2378-2398	UUACAAAGAGAA CUGGUUAGCCC	949	NM_016841.4_2376-2398_U1A_as	2376-2398
AD-526392.1	CUGACUCACUU UAUCAAUAGA	857	NM_016841.4_4668-4688_s	4668-4688	UCUAUUGAUAAA GUGAGUCAGCA	950	NM_016841.4_4666-4688_as	4666-4688
AD-526985.1	UUCUGUCUGUG AAUGUCUAUA	858	NM_016841.4_5438-5458_A21U_s	5438-5458	UAUAGACAUAUCA CAGACAGAAAAG	951	NM_016841.4_5436-5458_U1A_as	5436-5458
AD-527011.1	AUUGUGUGUUU UAACAAAUGA	859	NM_016841.4_5465-5485_A21U_s	5465-5485	UCAUUUGUUAAA ACACACAAUAC	952	NM_016841.4_5463-5485_U1A_as	5463-5485
AD-525341.1	UAUCUUGAAAU GCUUGUAAAA	860	NM_016841.4_3326-3346_G21U_s	3326-3346	UUUUACAAGCAU UUCAAGAUACA	953	NM_016841.4_3324-3346_C1A_as	3324-3346
AD-525265.1	GGAGCAGCUGA ACAUAUACAA	861	NM_016841.4_3180-3200_s	3180-3200	UUGUAUAUGUUC AGCUGCUCCAG	954	NM_016841.4_3178-3200_as	3178-3200
AD-527004.1	AUAGUGUAUUG UGUGUUUUAA	862	NM_016841.4_5458-5478_A21U_s	5458-5478	UUAAAACACACA AUACACUAUAU	955	NM_016841.4_5456-5478_U1A_as	5456-5478
AD-525336.1	GCAUGUAUCUU GAAAUGCUUA	863	NM_016841.4_3321-3341_G21U_s	3321-3341	UAAGCAUUUCAA GAUACAUGCUGU	956	NM_016841.4_3319-3341_C1A_as	3319-3341
AD-525353.1	CUUGUAAAGAG GUUUCUAACA	864	NM_016841.4_3338-3358_C21U_s	3338-3358	UGUUAGAAACCU CUUUACAAGCA	957	NM_016841.4_3336-3358_G1A_as	3336-3358
AD-525273.1	UGAACAUAUAC AUAGAUGUUA	865	NM_016841.4_3188-3208_G21U_s	3188-3208	UAACAUCUAUGU AUAUGUUCAGC	958	NM_016841.4_3186-3208_C1A_as	3186-3208
AD-524638.1	UCCACAGAAAC CCUGUUUUAA	866	NM_016841.4_2294-2314_s	2294-2314	UUAAAACAGGGU UUCUGUGGAGC	959	NM_016841.4_2292-2314_as	2292-2314
AD-526350.1	GGCUAGAUAGG AUAUACUGUA	867	NM_016841.4_4628-4648_A21U_s	4628-4648	UACAGUAUAUCC UAUCUAGCCCA	960	NM_016841.4_4626-4648_U1A_as	4626-4648

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-526962.1	CAUGAAAUCAU CUUAGCUUAA	868	NM_016841.4_5415-5435_G21U_s	5415-5435	UUAAGCUAAGAU GAUUUCAUGUC	961	NM_016841.4_5413-5435_C1A_as	5413-5435
AD-527005.1	UAGUGUAUUGU GUGUUUUA	869	NM_016841.4_5459-5479_C21U_s	5459-5479	UUUAAAACACAC AAUACACUAUA	962	NM_016841.4_5457-5479_G1A_as	5457-5479
AD-525269.1	CAGCUGAACAU AUACAUAGAA	870	NM_016841.4_3184-3204_s	3184-3204	UUCUAUGUAUUAU GUUCAGCUGCU	963	NM_016841.4_3182-3204_as	3182-3204
AD-524715.1	AGGGCUAACCA GUUCUCUUUA	871	NM_016841.4_2375-2395_G21U_s	2375-2395	UAAAGAGAACUG GUUAGCCCUGAA	964	NM_016841.4_2373-2395_C1A_as	2373-2395
AD-395454.1	AGGACGCAUGU AUCUUGAAAA	872	NM_001038609.2_3422-3442_s	3422-3442	UUUUCAAGAUAC AUGCGUCCUUU	965	NM_001038609.2_3420-3442_as	3420-3442
AD-525307.1	UGGAUUUGUCU GUUUUAUGCUA	873	NM_016841.4_3246-3266_s	3246-3266	UAGCAUAAAACAG ACAAAUCCAAC	966	NM_016841.4_3244-3266_as	3244-3266
AD-525352.1	GCUUGUAAAAGA GGUUUCUAAA	874	NM_016841.4_3337-3357_C21U_s	3337-3357	UUUAGAAAACCUC UUUACAAGCAU	967	NM_016841.4_3335-3357_G1A_as	3335-3357
AD-524641.1	ACAGAAACCCU GUUUUAUUGA	875	NM_016841.4_2297-2317_A21U_s	2297-2317	UCAAUAAAACAG GGUUUCUGUGG	968	NM_016841.4_2295-2317_U1A_as	2295-2317
AD-526297.1	CACGCUGGCUU GUGAUCUUAA	876	NM_016841.4_4528-4548_A21U_s	4528-4548	UUAAGAUCACAA GCCAGCGUGCC	969	NM_016841.4_4526-4548_U1A_as	4526-4548
AD-525268.1	GCAGCUGAACA UAUACAUAGA	877	NM_016841.4_3183-3203_A21U_s	3183-3203	UCUAUGUAUAUG UUCAGCUGCUC	970	NM_016841.4_3181-3203_U1A_as	3181-3203
AD-526997.1	AUGUCUAUAUA GUGUAUUGUA	878	NM_016841.4_5450-5470_G21U_s	5450-5470	UACAAUACACUA UAUAGACAUUC	971	NM_016841.4_5448-5470_C1A_as	5448-5470
AD-526991.1	CUGUGAAUGUC UAUAUAGUGA	879	NM_016841.4_5444-5464_s	5444-5464	UCACUAUAUAGA CAUUCACAGAC	972	NM_016841.4_5442-5464_as	5442-5464
AD-527012.1	UUGUGUGUUUU AACAAAUGAA	880	NM_016841.4_5466-5486_s	5466-5486	UUCAUUUGUUAA AACACACAAUA	973	NM_016841.4_5464-5486_as	5464-5486
AD-524720.1	UAACCAGUUCU CUUUGUAAGA	881	NM_016841.4_2380-2400_G21U_s	2380-2400	UCUUACAAAGAG AACUGGUUAGC	974	NM_016841.4_2378-2400_C1A_as	2378-2400
AD-525303.1	UAGUUGGAUUU GUCUGUUUAA	882	NM_016841.4_3242-3262_s	3242-3262	UUAAACAGACAA AUCCAACUACA	975	NM_016841.4_3240-3262_as	3240-3262
AD-526289.1	UGAAAAGGCAC GCUGGCUUGA	883	NM_016841.4_4520-4540_s	4520-4540	UCAAGCCAGCGU GCCUUUUCAAU	976	NM_016841.4_4518-4540_as	4518-4540
AD-526992.1	UGUGAAUGUCU AUUAUAGUGUA	884	NM_016841.4_5445-5465_A21U_s	5445-5465	UACACUAUAUAG ACAUUCACAGA	977	NM_016841.4_5443-5465_U1A_as	5443-5465
AD-525333.1	GACGCAUGUAU CUUGAAAUGA	885	NM_016841.4_3318-3338_C21U_s	3318-3338	UCAUUUCAAGAU ACAUGCGUCCU	978	NM_016841.4_3316-3338_G1A_as	3316-3338
AD-524335.1	CAACAAAGGAU UUGAAACUUA	886	NM_016841.4_1816-1836_G21U_s	1816-1836	UAAGUUUCAAU CCUUUGUUGCU	979	NM_016841.4_1814-1836_C1A_as	1814-1836
AD-526990.1	UCUGUGAAUGU CUAUUAUAGUA	887	NM_016841.4_5443-5463_G21U_s	5443-5463	UACUAUAUAGAC AUUCACAGACA	980	NM_016841.4_5441-5463_C1A_as	5441-5463

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-527006.1	AGUGUAUUGUG UGUUUUAACA	888	NM_016841.4_5460-5480_A21U_s	5460-5480	UGUUAAAACACA CAAUACACUAU	981	NM_016841.4_5458-5480_U1A_as	5458-5480
AD-526505.1	GAUUUCAACCA CAUUUGCUGAA	889	NM_016841.4_4842-4862_G21U_s	4842-4862	UUAGCAAAUGUG GUUGAAAUCAU	982	NM_016841.4_4840-4862_C1A_as	4840-4862
AD-525309.1	UUCACCAGAGU GACUAUGAUA	890	NM_001038609.2_3338-3358_s	3338-3358	UAUCAUAGUCAC UCUGGUGAAUC	983	NM_016841.4_3268-3290_U1A_as	3336-3358
AD-524328.1	GUGGCAGCAAC AAAGGAUUUA	891	NM_016841.4_1809-1829_G21U_s	1809-1829	UAAAUCCUUUGU UGCUGCCACUG	984	NM_016841.4_1807-1829_C1A_as	1807-1829
AD-395455.1	GGACGCAUGUA UCUUGAAUA	892	NM_001038609.2_3423-3443_s	3423-3443	UAUUUCAAGUA CAUGCGUCCUU	985	NM_001038609.2_3421-3443_as	3421-3443
AD-526428.1	UAUCCUGUUUG CUAUUGCUGUA	893	NM_016841.4_4720-4740_G21U_s	4720-4740	UAAGCAAUAGCA AACAGGAUACA	986	NM_016841.4_4718-4740_C1A_as	4718-4740
AD-526847.1	UUCUCUUCAGC UUUGAAAAGA	894	NM_016841.4_5259-5279_G21U_s	5259-5279	UCUUUCAAAGC UGAAGAGAAAU	987	NM_016841.4_5257-5279_C1A_as	5257-5279
AD-525957.1	UCUGGUUUGGG UACAGUUAUA	895	NM_016841.4_4084-4104_A21U_s	4084-4104	UUUAAACUGUACC CAAACCAGAAAG	988	NM_016841.4_4082-4104_U1A_as	4082-4104
AD-524332.1	CAGCAACAAAG GAUUUGAAAA	896	NM_016841.4_1813-1833_C21U_s	1813-1833	UUUUCAAAUCCU UUGUUGCUGCC	989	NM_016841.4_1811-1833_G1A_as	1811-1833
AD-526291.1	AAAAGGCACGC UGGCUUGUGA	897	NM_016841.4_4522-4542_A21U_s	4522-4542	UCACAAGCCAGC GUGCCUUUUA	990	NM_016841.4_4520-4542_U1A_as	4520-4542
AD-526485.1	UGCCUCGUAAC CCUUUUAUA	898	NM_016841.4_4822-4842_G21U_s	4822-4842	UAUGAAAAGGGU UACGAGGCAGU	991	NM_016841.4_4820-4842_C1A_as	4820-4842
AD-526292.1	AAAGGCACGCU GGCUUGUGAA	899	NM_016841.4_4523-4543_s	4523-4543	UUCACAAGCCAG CGUGCCUUUUC	992	NM_016841.4_4521-4543_as	4521-4543
AD-524642.1	CAGAAACCCUG UUUUUAUUGAA	900	NM_016841.4_2298-2318_G21U_s	2298-2318	UUCAAUAAAACA GGGUUUCUGUG	993	NM_016841.4_2296-2318_C1A_as	2296-2318
AD-526290.1	GAAGGCACGCG CUGGCUUGUA	901	NM_016841.4_4521-4541_G21U_s	4521-4541	UACAAGCCAGCG UGCCUUUCAA	994	NM_016841.4_4519-4541_C1A_as	4519-4541
AD-525959.1	UGGUUUGGGUA CAGUUAAGA	902	NM_016841.4_4086-4106_G21U_s	4086-4106	UCUUUAAACUGUA CCCAAACCAGA	995	NM_016841.4_4084-4106_C1A_as	4084-4106
AD-526293.1	AAGGCACGCG GCUUGUGAUA	903	NM_016841.4_4524-4544_C21U_s	4524-4544	UAUCACAAGCCA GCGUGCCUUUU	996	NM_016841.4_4522-4544_G1A_as	4522-4544
AD-524899.1	CAUACUGAGGG UGAAAUUAAA	904	NM_016841.4_2668-2688_G21U_s	2668-2688	UUUAAUUUCACC CUCAGUAUGGA	997	NM_016841.4_2666-2688_C1A_as	2666-2688
AD-526391.1	GCUGACUCACU UUAUCAAUA	905	NM_016841.4_4667-4687_G21U_s	4667-4687	UUAUUGAUAAAG UGAGUCAGCAG	998	NM_016841.4_4665-4687_C1A_as	4665-4687
AD-525956.1	UUCUGGUUUGG GUACAGUUA	906	NM_016841.4_4083-4103_A21U_s	4083-4103	UUAACUGUACCC AAACCAGAAGU	999	NM_016841.4_4081-4103_U1A_as	4081-4103

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_016841.4
AD-525958.1	CUGGUUUGGGU ACAGUAAAAA	907	NM_016841.4_4085-4105_G21U_s	4085-4105	UUUUUACUGUAC CCAAACCAGAA	1000	NM_016841.4_4083-4105_C1A_as	4083-4105
AD-526351.1	GCUAGAUAGGA UAUACUGUAA	908	NM_016841.4_4629-4649_s	4629-4649	UUACAGUAUAUC CUAUCUAGCCC	1001	NM_016841.4_4627-4649_as	4627-4649
AD-526138.1	CUCAUUCUGC CAACAGUUUA	909	NM_016841.4_4329-4349_C21U_s	4329-4349	UAAACUGUUGGC AGUAAUGAGGG	1002	NM_016841.4_4327-4349_G1A_as	4327-4349
AD-524898.1	CCAUACUGAGG GUGAAAUUAA	910	NM_016841.4_2667-2687_A21U_s	2667-2687	UUAAUUUCACCC UCAGUAUGGAG	1003	NM_016841.4_2665-2687_U1A_as	2665-2687
AD-526244.1	CAGCCUAAGAU CAUGGUUUAA	911	NM_016841.4_4475-4495_G21U_s	4475-4495	UUAAACCAUGAU CUUAGGCUGGC	1004	NM_016841.4_4473-4495_C1A_as	4473-4495
AD-525359.1	AAGAGGUUUCU AACCCACCCA	912	NM_016841.4_3344-3364_s	3344-3364	UGGGUGGGUUAG AAACCUCUUUA	1005	NM_016841.4_3342-3364_as	3342-3364
AD-526393.1	UGACUCACUUU AUCAAUAGUA	913	NM_016841.4_4669-4689_s	4669-4689	UACUAUUGAUAA AGUGAGUCAGC	1006	NM_016841.4_4667-4689_as	4667-4689
AD-525355.1	UGUAAAAGAGGU UUCUAAACCCA	914	NM_016841.4_3340-3360_A21U_s	3340-3360	UGGGUUAGAAAC CUCUUUACAAG	1007	NM_016841.4_3338-3360_U1A_as	3338-3360
AD-526288.1	UUGAAAAGGCA CGCUGGCUUA	915	NM_016841.4_4519-4539_G21U_s	4519-4539	UAAGCCAGCGUG CCUUUCAAUU	1008	NM_016841.4_4517-4539_C1A_as	4517-4539
AD-524897.1	UCCAUACUGAG GGUGAAAUA	916	NM_016841.4_2666-2686_A21U_s	2666-2686	UAAUUUCACCCU CAGUAUGGAGU	1009	NM_016841.4_2664-2686_U1A_as	2664-2686
AD-526796.1	GAUACCUGCG UGUCCCAUCA	917	NM_016841.4_5208-5228_s	5208-5228	UGAUGGGACACG CAGGUGAUCAC	1010	NM_016841.4_5206-5228_as	5206-5228
AD-526295.1	GGCACGCUGGC UUGUGAUCUA	918	NM_016841.4_4526-4546_s	4526-4546	UAGAUCACAAGC CAGCGUGCCUU	1011	NM_016841.4_4524-4546_as	4524-4546
AD-526294.1	AGGCACGCUGG CUUGUGAUCUA	919	NM_016841.4_4525-4545_s	4525-4545	UGAUCACAAGCC AGCGUGCCUUU	1012	NM_016841.4_4523-4545_as	4523-4545
AD-525356.1	GUAAAGAGGUU UCUAAACCCA	920	NM_016841.4_3341-3361_C21U_s	3341-3361	UUGGGUUAGAAA CCUCUUUACAA	1013	NM_016841.4_3339-3361_G1A_as	3339-3361

Table 6. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 1

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-523799.1	asusagucUfaCfAfAf accaguugaal96	163	VPusUfscacCfuGfGfuuu gUfaGfacuauusu	238	AAAUAGUCUACAAACC AGUUGAC	313
AD-523802.1	gsuscuacAfaAfCfCf aguugaccuaL96	164	VPusAfsgguCfaAfCfug guUfuGfuagacsusa	239	UAGUCUACAAACCAGU UGACCUG	314
AD-523795.1	gsesaaauAfgUfCfUf acaaaccagaL96	165	VPusCfsuggUfuUfGfua gaCfuAfuuugcsasc	240	GUGCAAAUAGUCUACA AACCAGU	315
AD-523810.1	ascscaguUfgAfCfCf ugagcaaggaL96	166	VPusCfscuuGfcUfCfagg uCfaAfcuggususu	241	AAACCAGUUGACCUGA GCAAGGU	316
AD-523809.1	asasccagUfuGfAfCf cugagcaagaL96	167	VPusCfsuugCfuCfAfagg ucAfaCfugguusug	242	CAAACCAGUUGACCUG AGCAAGG	317
AD-1019331.1	usgscaaaUfaGfUfCf uacaaaccaal96	168	VPusUfsgguUfuGfufag acUfaUfuugcsaca	243	AGGUGCAAAUAGUCU ACAAACCA	318

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-523801.1	asgsucuaCfaAfAfCf caguugaccaL96	169	VPusGfsgucAfaCfUfgg uuUfgUfagacusasu	244	AUAGUCUACAAACCAG UUGACCU	319
AD-523823.1	asgscaagGfuGfAfCf cuccaagugaL96	170	VPusCfsacuUfgGfAfgg ucAfcCfuugcuscasa	245	UGAGCAAGGUGACCUC CAAGUGU	320
AD-523798.1	asasuaguCfuAfCfAf aaccaguugaL96	171	VPusCfsaacUfgGfUfuug uAfgAfcuauusug	246	CAAAUAGUCUACAAAC CAGUUGA	321
AD-523816.1	usgsaccuGfaGfCfAf aggugaccuaL96	172	VPusAfsnguCfaCfCfuug cUfcAfggucasasc	247	GUUGACCUGAGCAAGG UGACCUC	322
AD-523824.1	gsesaaggUfgAfCfCf uccaaguguaL96	173	VPusAfscauUfuGfGfagg uCfaCfcuugcsusc	248	GAGCAAGGUGACCUCC AAGUGUG	323
AD-523800.1	usasgucuAfcAfAfA fccaguugacaL96	174	VPusGfsucaAfcUfGfgu uuGfuAfgacuusu	249	AAUAGUCUACAAACCA GUUGACC	324
AD-523796.1	csasaauaGfuCfUfAf caaaccaguaL96	175	VPusAfsacugGfuUfUfgu agAfcUfauuugscsa	250	UGCAAAUAGUCUACAA ACCAGUU	325
AD-523803.1	uscsuacaAfaCfCfAf guugaccugaL96	176	VPusCfsaggUfcAfAfcug gUfuUfguagascsu	251	AGUCUACAAACCAGUU GACCUGA	326
AD-523817.1	gsasecugAfgCfAfA fggugaccuaL96	177	VPusGfsaggUfcAfCfcuu gCfuCfagguacsasa	252	UUGACCUGAGCAAGGU GACCUCC	327
AD-523825.1	csasagguGfaCfCfUf ccaagugugaL96	178	VPusCfsacaCfuUfGfgag gUfcAfcuugscsu	253	AGCAAGGUGACCUCCA AGUGUGG	328
AD-523811.1	cscsaguuGfaCfCfUf gagcaagguaL96	179	VPusAfsccuUfgCfUfcag gUfcAfacuugscsu	254	AACCAGUUGACCUGAG CAAGGUG	329
AD-523854.1	gsagsaacAfuCfCfAf ucauaaaccal96	180	VPusGfsguuUfaUfGfau ggAfuGfuugccsusa	255	UAGGCAACAUCUCAUC UAAACCA	330
AD-523797.1	asasauagUfcUfAfCf aaaccaguuaL96	181	VPusAfsacuGfgUfUfug uaGfaCfuauuugsc	256	GCAAAUAGUCUACAAA CCAGUUG	331
AD-523805.1	usascaaaCfcAfGfUf ugaccugagaL96	182	VPusCfsucaGfgUfCfaac uGfgUfuuguasgsa	257	UCUACAAACCAGUUGA CCUGAGC	332
AD-523814.1	gsusugacCfuGfAfG fcaaggugacaL96	183	VPusGfsucaCfcUfUfgcu cAfgGfucaacsug	258	CAGUUGACCUGAGCAA GGUGACC	333
AD-523804.1	csusacaaAfcCfAfGf uugaccugaaL96	184	VPusUfscagGfuCfAfacu gGfuUfuguasgsa	259	GUCUACAAACCAGUUG ACCUGAG	334
AD-1019356.1	gsusugucAfaAfUfA fgucuacaaaL96	185	VPusUfsuugUfaGfAfcu auUfuGfcacacsug	260	CAGUGUGCAAAUAGUC UACAAAC	335
AD-523846.1	gsesucuuUfaGfGfCf aacaucuaL96	186	VPusAfsuggAfuGfUfug ccUfaAfuagcscsa	261	UGGCUCAUUAAGGCAAC AUCCAUC	336
AD-523808.1	asasaccaGfuUfGfAf ccugagcaaaL96	187	VPusUfsgucUfcAfGfgu caAfcUfgguusgsu	262	ACAAACCAGUUGACCU GAGCAAG	337
AD-523835.1	cscsaaguGfuGfGfCf ucauuaggcaL96	188	VPusGfscuuAfaUfGfagc cAfcAfcuuggsasg	263	CUCCAAGUGUGGCUCA UUAGGCA	338
AD-1019357.1	usgsugcaAfaUfAfG fucuacaaacaL96	189	VPusGfsuuuGfuAfGfac uaUfuUfgcacascsu	264	AGUGUGCAAAUAGUC UACAAACC	339
AD-523853.1	asgsgecaCfaUfCfCf aucauaaacaL96	190	VPusGfsuuuAfuGfAfug gaUfgUfugccusasa	265	UUAGGCAACAUCCAUC AUAAACC	340
AD-523819.1	cscsugagCfaAfGfGf ugaccuccaaL96	191	VPusUfsggaGfgUfCfacc uUfgCfucaggsusc	266	GACCUGAGCAAGGUGA CCUCCAA	341
AD-523830.1	gsasecuCfaAfGfUf guggcucauaL96	192	VPusAfsugaGfcCfAfcac uUfgGfagguacsasc	267	GUGACCUCCAAGUGUG GCUCAUU	342
AD-523834.1	usescaggUfgUfGfG fcucauuaggal96	193	VPusCfscuaAfuGfAfgcc aCfaCfuuggsasg	268	CCUCCAAGUGUGGCUC AUUAGGC	343
AD-523850.1	asusuaggCfaAfCfAf uccaucauaaL96	194	VPusUfsaugAfuGfGfau guUfgCfcuaausgsa	269	UCAUUAGGCAACAUC AUCAUAA	344
AD-523820.1	csusgagCfaGfGfU fgaccuccaaaL96	195	VPusUfsuggAfgGfUfca ccUfuGfcucagsgsu	270	ACCUGAGCAAGGUGAC CUCCAAG	345
AD-523849.1	csasuagGfcAfAfCf auccaucauaL96	196	VPusAfsugaUfgGfAfug uuGfcCfuauusgsa	271	CUCAUUAGGCAACAUC CAUCAUA	346

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-523845.1	gsgscucaUfuAfGfGfcaacaucacaaL96	197	VPusUfsggaUfgUfUfgc cuAfaUfgagccsasc	272	GUGGCUCAUUAGGCAA CAUCCAU	347
AD-393758.3	asgsugugCfaAfAfUfagucuacaaaL96	198	VPusUfsuguAfgAfCfua uuUfgCfacacusgsc	273	GCAGUGUGCAAUAG UCUACAAG	348
AD-523848.1	uscsauuaGfgCfAfAfcuuccaucaL96	199	VPusUfsgauGfgAfUfgu ugCfcUfaugagsgsc	274	GCUCAUUAGGCAACAU CCAUCAU	349
AD-523840.1	asgsugugGfcUfCfAfuaggaacaL96	200	VPusGfsuugCfcUfAfau gaGfcCfacacusug	275	CAAGUGUGGCUCAUUA GGCAACA	350
AD-523828.1	gsgsugacCfuCfCfA aguguggcuaL96	201	VPusAfsgccAfcAfCfuug gAfgGfucacsusu	276	AAGGUGACCUCCAAGU GUGGCUC	351
AD-523822.1	gsasgcaaGfgUfGfAfcuccaagaaL96	202	VPusAfsuuGfgAfGfgu caCfcUfugcuscasg	277	CUGAGCAAGGUGACCU CCAAGUG	352
AD-523806.1	ascsaaacCfaGfUfUfgaccugagcaL96	203	VPusGfscucAfgGfUfcaa cUfgGfuugusag	278	CUACAAACCAGUUGAC CUGAGCA	353
AD-523831.1	ascsuccAfaGfUfGfuggcucuuL96	204	VPusAfsaugAfgCfCfaca cUfuGfgaguscasa	279	UGACCUCCAAGUGUGG CUCAUUA	354
AD-393757.1	csasguguGfcAfAfAfuagucuacaaL96	205	VPusUfsguaGfaCfUfauu uGfcAfcacusgsc	280	GGCAGUGUGCAAUA GUCUACAA	355
AD-523839.1	asasguguGfgCfUfCfauuaggcaaaL96	206	VPusUfsgucCfuAfAfug agCfcAfcacuusgsg	281	CCAAGUGUGGCUCAU AGGCAAC	356
AD-523815.1	usugaccUfgAfGfCfaagguagcaL96	207	VPusGfsgucAfcCfUfugc uCfaGfgucaacsu	282	AGUUGACCUGAGCAAG GUGACCU	357
AD-523856.1	csasacauCfcAfUfCfauaaaccagaL96	208	VPusCfsuggUfuUfAfug auGfgAfuguugscsc	283	GGCAACAUCCAUCAUA AACCAGG	358
AD-1019330.1	gsusgcaaAfuAfGfUfcuacaaaccaL96	209	VPusGfsguuUfgUfAfga cuAfuUfugcacsasc	284	AGGUGCAAUAGUCU ACAAAACA	359
AD-523829.1	usgsaccuCfcAfAfGfUguggcucuaL96	210	VPusUfsgagCfcAfCfacu uGfgAfggucascsc	285	GGUGACCUCCAAGUGU GGCUCAU	360
AD-523855.1	gcsaacaUfcCfAfUfcauaaaccacL96	211	VPusUfsgguUfuUfUfga ugGfaUfguugcsesu	286	AGGCAACAUCCAUCAU AAACCAG	361
AD-523836.1	csasagugUfgGfCfUfcuauaggcaL96	212	VPusUfsgccUfaAfUfgag cCfaCfacuugsgsa	287	UCCAAGUGUGGCUCAU UAGGCAA	362
AD-1019329.1	gscsagugUfgCfAfAfaugucuacL96	213	VPusGfsuagAfcUfAfuu ugCfaCfagucscsg	288	GCAGUGUGCAAUAG UCUACA	363
AD-523843.1	gsusggcuCfaUfUfAfggcaacaL96	214	VPusGfsaugUfuGfCfua aUfgAfgccacsasc	289	GUGUGGCUCAUAGGC AACAUCC	364
AD-523807.1	csasaaccAfgUfUfGfaccugagcaL96	215	VPusUfsgcuCfaGfGfuca aCfuGfguuugsusa	290	UACAAACCAGUUGACC UGAGCAA	365
AD-523821.1	usgsagcaAfgGfUfGfaccuccaagaL96	216	VPusCfsuugGfaGfGfuca cCfuUfgcucasgsg	291	CCUGAGCAAGGUGACC UCCAAGU	366
AD-523826.1	asasggugAfcCfUfCfcaaguguggaL96	217	VPusCfsacAfcUfUfgga gGfuCfaccuusgsc	292	GCAAGGUGACCUCCAA GUGUGGC	367
AD-523847.1	csuscauuAfgGfCfAfacuuccaucaL96	218	VPusGfsaugGfaUfGfuu gcCfuAfaugagscsc	293	GGCUCAUAGGCAACA UCCAUCA	368
AD-523786.1	gsusgaccUfcCfAfAfguguggcuaL96	219	VPusGfsagcCfaCfAfcuu gGfaGfgucacsesu	294	AGGUGACCUCCAAGUG UGGCUCA	369
AD-523812.1	csasguugAfcCfUfGfagcaaggugaL96	220	VPusCfsaccUfuGfCfuca gGfuCfaacugsgsu	295	ACCAGUUGACCUGAGC AAGGUGA	370
AD-523827.1	asgsugugaCfcUfCfAaaguguggaL96	221	VPusGfscacCfaCfUfugg aGfgUfcaccusug	296	CAAGGUGACCUCCAAG UGUGGCU	371
AD-523844.1	usgsgeucAfuUfAfGfgcaacaaccaL96	222	VPusGfsgauGfuUfGfcc uaAfuGfgaccascsa	297	UGUGGCUCAUAGGCA ACAUCCA	372
AD-523851.1	ususaggeAfaCfAfUfcucauaaaaL96	223	VPusUfsuauGfaUfGfga ugUfuGfccuaasug	298	CAUUAAGGCAACAUCCA UCAUAAA	373
AD-523818.1	ascsaugaGfcAfAfGfgugaccuccaL96	224	VPusGfsgagGfuCfAfcuu uGfcUfcagguscasa	299	UGACCUGAGCAAGGUG ACCUCCA	374

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-523832.1	cscsucCaAfgUfGfUf ggcucauuuaL96	225	VPusUfsaaUgfaGfCfcac aCfuUfggaggsusc	300	GACCUCCAAGUGUGGC UCAUUAG	375
AD-523813.1	asgsuugaCfcUfGfA fgcaaggugaaL96	226	VPusUfscacCfuUfGfcuc aGfgUfcaacugsg	301	CCAGUUGACCUGAGCA AGGUGAC	376
AD-523841.1	gsusgugCfuCfAfU fuaggcaacaaL96	227	VPusUfsguuGfcCfuFaaU gAfgCfcacacsusu	302	AAGUGUGGCUCAUUA GGCAACAU	377
AD-1019352.1	asgsgcgCfaGfUfG fugcaaaugaL96	228	VPusCfsuauUfuGfCfaca cUfgCfcgcccusc	303	GGAGGCGGCAGUGUGC AAAUAGU	378
AD-1019354.1	gscsggcaGfuGfUfG fcaaauguaL96	229	VPusGfsacuAfuUfUfgca cAfcUfgccgcsesu	304	AGGCGGCAGUGUGCAA AUAGUCU	379
AD-523852.1	usasggcaAfcAfUfCf caucaaaaaL96	230	VPusUfsuuaUfgAfUfgg auGfuUfgcuasasu	305	AUUAGGCAACAUCCAU CAUAAAC	380
AD-523842.1	usgsugcUfcAfUfU faggcaacauaL96	231	VPusAfsuguUfgCfCfuua uGfaGfccacacsu	306	AGUGUGGCUCAUUAG GCAACAUC	381
AD-523833.1	csusccaaGfuGfUfGf gcucauuagaL96	232	VPusCfsuuaUfgAfGfcca cAfcUfuggaggsu	307	ACCUCCAAGUGUGGCU CAUUAGG	382
AD-1019328.1	gsgscaguGfuGfCfA faauagucuaL96	233	VPusUfsagaCfuAfUfuU gcAfcAfcugccsgsc	308	GCGGCAGUGUGCAAU AGUCUAC	383
AD-1019355.1	csgsgcagUfgUfGfC faaaugucuaL96	234	VPusAfsagCfuAfUfugc aCfaCfugccgcsesu	309	GGCGGCAGUGUGCAA UAGUCUA	384
AD-1019353.1	gsgsgcgCfaGfUfGfU fgcaaaugaL96	235	VPusAfsuuaUfuUfGfcac aCfuGfcgcccusc	310	GAGGCGGCAGUGUGCA AAUAGUC	385
AD-1019350.1	gsgsagcGfgCfAfG fugugcaauaL96	236	VPusAfsuuuGfcAfCfacu gCfcGfccuccscsg	311	CGGGAGGCGGCAGUGU GCAAAUA	386
AD-1019351.1	gsasggcGfcAfGfU fugcaaaualL96	237	VPusUfsauuUfgCfAfcac uGfcCfcgcccusc	312	GGGAGGCGGCAGUGU GCAAAUAG	387

Table 7. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 2

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-535094.1	asgscucGfaUfGfGfuca guaaaaaL96	564	VPusUfsuuua(Cgn)ug accaUfgCfagcuscusg	652	CAAGCUCGCAUGG UCAGUAAAAG	740
AD-535095.1	gscsucgcAfuGfGfUfcag uaaaagaL96	565	VPusCfsuuuu(Agn)cu gaccAfuGfagcuscusu	653	AAGCUCGCAUGGU CAGUAAAAGC	741
AD-538647.1	usasuuuGfuGfUfUfuua acaaauaL96	566	VPusAfsuuug(Tgn)uaa aacAfcAfcuaascsa	654	UGUAUUGUGUGUU UUAACAAAG	742
AD-535922.1	csasgcaaCfaAfAfGfgau uugaaaaL96	567	VPusUfsuua(Cgn)auc cuuUfgUfugcugscsc	655	GGCAGCAACAAAG GAUUUGAAAC	743
AD-536317.1	gscsuuacCfaGfUfUfcuc uuuguuaL96	568	VPusUfsaaca(Agn)gag aacUfgGfuuagcscsc	656	GGGCUAACCAGUU CUCUUUGUAA	744
AD-536911.1	usasguuGfaUfUfUfguc uguuuuaL96	569	VPusUfsaaac(Agn)gac aaaUfcCfaacuascsa	657	UGUAGUUGGAUUU GUCUGUUUAU	745
AD-538626.1	gsuscuguGfaAfUfGfucu auauagaL96	570	VPusCfsuaua(Tgn)aga cauUfcAfcagacsag	658	CUGUCUGUGAAUG UCUAUUAUAGU	746
AD-535864.1	csasggcaAfuUfCfCfuuu ugauucaL96	571	VPusGfsaauc(Agn)aaa ggaAfuUfgcugcsag	659	CUCAGGCAAUUCCU UUUGAUUCU	747
AD-535925.1	csasacaaAfgGfAfUfuug aaacuuaL96	572	VPusAfsagu(Tgn)caa aucCfuUfuguuagcsu	660	AGCAACAAAGGAU UUGAAACUUG	748
AD-538012.1	gscsugacUfcAfCfUfuua ucaauuaL96	573	VPusUfsauug(Agn)ua aaguGfaGfucagcsag	661	CUGCUGACUCACUU UAUCAAUAG	749
AD-536872.1	gscsagcuGfaAfCfAfua acaauagaL96	574	VPusCfsuauug(Tgn)aua uguUfcAfcugcsusc	662	GAGCAGCUGAACA UAUACAUAAGA	750
AD-536954.1	asgsgacGfaUfGfUfauc uugaaaaL96	575	VPusUfsuua(Cgn)ga uacaUfgCfugccuscusu	663	AAAGGACGCAUGU AUCUUGAAAU	751

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-536964.1	usasucuuGfaAfAfUfgcu uguaaaaL96	576	VPusUfsuuac(Agn)agc auuUfcAfagauascsa	664	UGUAUCUUGAAA GCUUGUAAAAG	752
AD-536318.1	csusaaccAfgUfUfCfucu uuguuaaL96	577	VPusUfsuaca(Agn)aga gaaCfuGfguuagscsc	665	GGCUAACAGUUC UCUUGUAAG	753
AD-536976.1	csusuguaAfaGfAfGfguu ucuacaL96	578	VPusGfsuuag(Agn)aac cucUfuUfacaagscsc	666	UGCUUGUAAAAGAG GUUUCUAACC	754
AD-538630.1	gsusgaaUGfuCfUfAfua aguguaaL96	579	VPusUfsuac(Tgn)aua uagAfcAfuucacsasg	667	CUGUGAAUGUCUA UAUAGUGUAU	755
AD-538624.1	csusgucuGfuGfAfAfugu cuauuaL96	580	VPusAfsuaua(Ggn)aca uucAfcAfgacagsasa	668	UUCUGUCUGUGAA UGUCUAUAUA	756
AD-538594.1	asgsaggacAfuGfAfAfauc aucuuaL96	581	VPusUfsaaga(Tgn)gau uucAfuGfuccuscsc	669	GGAGGGACAUGAA AUAUCUUAG	757
AD-536915.1	usgsgauUfgUfCfUfguu uauuguaL96	582	VPusAfsagcau(Agn)aac agaCfaAfauccasasc	670	GUUGGAUUUGUCU GUUUAUGCUU	758
AD-536870.1	gsasgcagCfuGfAfAfcau auacuaL96	583	VPusAfsugua(Tgn)aug uucAfgCfugcuscsc	671	UGGAGCAGCUGAA CAUAUACAU	759
AD-536236.1	ascagaaAfcCfCfUfguu uuauugaL96	584	VPusCfsaua(Agn)aac aggGfuUfucugusgsg	672	CCACAGAAACCCUG UUUUAUUGA	760
AD-536319.1	usasaccaGfuUfCfUfcuu uguuaaL96	585	VPusCfsuuac(Agn)aag agaAfcUfgguuasgsc	673	GCUAACAGUUCUC UUUGUAAGG	761
AD-536966.1	uscsuugaAfaUfGfCfuug uaaagaaL96	586	VPusUfscuuu(Agn)caa gcaUfuUfcaagasusa	674	UAUCUUGAAUUGC UUGUAAAAGAG	762
AD-538643.1	asgsuguaUfuGfUfGfugu uuuaacaL96	587	VPusGfsuuua(Agn)aca cacAfaUfacacusasu	675	AUAGUGUAUUGUG UGUUUUAACA	763
AD-536873.1	csasgcugAfaCfAfUfaua cauagaaL96	588	VPusUfscuau(Ggn)ua uugUfuCfagcugscsu	676	AGCAGCUGAACAU AUACAUAGAU	764
AD-536952.1	asasaggaCfgCfAfUfgua ucuugaaL96	589	VPusUfscuag(Agn)uac augCfgUfcuuususu	677	AAAAAGGACGCAU GUAUCUUGAA	765
AD-536959.1	gscsauguAfuCfUfUfgaa augcuuaL96	590	VPusAfsagca(Tgn)uuc aagAfuAfcuagcsgsu	678	ACGCAUGUAUCUU GAAAUGCUUG	766
AD-537921.1	ascsgcugGfcUfUfGfuga ucuuaaaL96	591	VPusUfsuuaag(Agn)uca caaGfcCfagcugsgsc	679	GCACGCUGGCUUG UGAUCUUAUA	767
AD-538652.1	usuuuaaCfaAfAfUfgau uuacacaL96	592	VPusGfsugua(Agn)au cauuUfgUfuaaaascsa	680	UGUUUUAACAAAU GAUUUACACU	768
AD-538649.1	usuguguGfuUfUfUfaac aaauagaaL96	593	VPusUfscuuu(Tgn)guu aaaAfcAfcuaasusa	681	UAUUGUGUUUUU AACAAUAGAU	769
AD-538623.1	uscsgucUfgUfGfAfaug ucuuaaaL96	594	VPusUfsauag(Agn)cau ucaCfaGfagagasasa	682	UUUCUGUCUGUGA AUGUCUAUAU	770
AD-538573.1	gscsaaguCfcCfAfUfgau uucuucaL96	595	VPusGfsaaga(Agn)auc augGfgAfcuugesasa	683	UUGCAAGUCCCAU GAUUUCUUCG	771
AD-537920.1	csascgcuGfgCfUfUfgug aucuuaaL96	596	VPusUfsaaga(Tgn)cac aagCfcAfgcugsgsc	684	GGCACGCUGGCUU GUGAUCUUAU	772
AD-536939.1	ususcaccAfgAfGfUfgac uauagaaL96	597	VPusAfsucau(Agn)gu cacuUfuGfgugaasusc	685	GAUUCACCAGAGU GACUAUGAUA	773
AD-538015.1	gsascucaCfuUfUfAfuca auaguuaL96	598	VPusAfsacua(Tgn)uga uaaAfgUfgagucsasg	686	CUGACUCACUUAU UCAAUAGUUC	774
AD-536953.1	asasggacGfcAfUfGfuau cuugaaaL96	599	VPusUfsucau(Ggn)aua cauGfcGfuccuususu	687	AAAAGGACGCAUG UAUCUUGAAA	775
AD-536237.1	csasgaaaCfcCfUfGfuuu uauugaaL96	600	VPusUfscuuu(Agn)aaa cagGfgUfuucugsusg	688	CACAGAAACCCUGU UUUAUUGAG	776
AD-538628.1	csusgugaAfuGfUfCfuau auagugaL96	601	VPusCfsacua(Tgn)aua gacAfuUfcacagsasc	689	GUCUGUGAAUGUC UAUAUAGUGU	777
AD-538632.1	gsasauguCfuAfUfAfua uguaauaL96	602	VPusAfsauac(Agn)cua uauAfgAfcuucasc	690	GUGAAUGUCUAUA UAGUGUAUUG	778
AD-536975.1	gscsuuguAfaAfGfAfggu uucuaaaL96	603	VPusUfsuaga(Agn)acc ucuUfuAfcuagcsasu	691	AUGCUUGUAAAGA GGUUUCUAAC	779

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-538599.1	csasugaaAfuCfAfUfcuu agcuuaaL96	604	VPusUfsaagc(Tgn)aag augAfuUfucugsusc	692	GACAUGAAAUCAU CUUAGCUUAG	780
AD-536978.1	usgsuaaaGfaGfGfUfuuc uaaccaL96	605	VPusGfsgguu(Agn)ga aaccUfcUfuucasasg	693	CUUGUAAAGAGGU UUCUAACCCA	781
AD-536956.1	gsascgcaUfgUfAfUfcuu gaaaugaL96	606	VPusCfsauuu(Cgn)aag auaCfaUfgcgucscsu	694	AGGACGCAUGUAU CUUGAAAUGC	782
AD-538571.1	ususgcaaGfuCfCfCfaug auuucuaL96	607	VPusAfsghaa(Tgn)cau gggAfcUfugcaasgsu	695	ACUUGCAAAGUCCCA UGAUUUCUU	783
AD-535921.1	gscsagcaAfcAfAfAfgga uuugaaaL96	608	VPusUfsucaa(Agn)ucc uuuGfuUfgcgucscsa	696	UGGCAGCAACAAA GGAUUUGAAA	784
AD-538593.1	gsasgggaCfaUfGfAfaau caucuaaL96	609	VPusAfsagau(Ggn)au uuaUfgUfcccucscsc	697	GGGAGGGACAUGA AAUCAUCUUA	785
AD-537974.1	gscsuagaUfaGfGfAfaau acuguaaL96	610	VPusUfsacag(Tgn)aua uccUfaUfcuagcscsc	698	GGGCUAGAUAGGA UAUACUGUAU	786
AD-537973.1	gsgscuagAfuAfGfGfaaa uacuguaL96	611	VPusAfsagau(Agn)ua uccuAfuCfuagccscsa	699	UGGCUAGAUAGG AUUACUGUA	787
AD-536982.1	asasgaggUfuUfCfUfaac ccaccaL96	612	VPusGfsggug(Ggn)gu uagaAfaCfcuucususa	700	UAAAGAGGUUUCU AACCCACCCU	788
AD-535918.1	gsusggcaGfcAfAfCfaaa ggauuaaL96	613	VPusAfsaauc(Cgn)uuu guuGfcUfgccacsug	701	CAGUGGCAGCAAC AAAGGAUUUG	789
AD-538627.1	uscsugugAfaUfGfUfcua uauaguaL96	614	VPusAfscauu(Agn)ua gacaUfuCfacagascsa	702	UGUCUGUGAAUGU CUAUUAGUG	790
AD-536913.1	gsusuggaUfuUfGfUfcug uuuaugaL96	615	VPusCfsauaa(Agn)cag acaAfaUfccacsusa	703	UAGUUGGAUUUGU CUGUUUAGUC	791
AD-536869.1	gsgsagcaGfcUfGfAfaaa uauacaaL96	616	VPusUfsguau(Agn)ug uuaGfcUfgcuccsasg	704	CUGGAGCAGCUGA ACAUUACAU	792
AD-536965.1	asuscugAfaAfUfGfcuu guaaagaL96	617	VPusCfsuuua(Cgn)aag cauUfuCfaagausasc	705	GUAUCUUGAAAUG CUUGUAAAAGA	793
AD-537914.1	asasaaggCfaCfGfCfugg cuuguaL96	618	VPusCfsacaa(Ggn)cca gagUfgCfcuuuucsa	706	UGAAAAGGCACGC UGGCUUGUGA	794
AD-536504.1	cscsauacUfgAfGfGfgug aaauuaaL96	619	VPusUfsaaui(Tgn)cac ccuCfaGfuaggsasg	707	CUCCAUAUGAGG GUGAAAUUAA	795
AD-538013.1	csusgacuCfaCfUfUfuau cauagaL96	620	VPusCfsuauu(Ggn)aua aagUfgAfgucagscsa	708	UGCUGACUCACUU UAUCAAUAGU	796
AD-537579.1	ususcuggUfuUfGfGfgua caguuaaL96	621	VPusUfsaacu(Ggn)uac ccaAfaCfcagaasgsu	709	ACUUCUGGUUUGG GUACAGUUAA	797
AD-538629.1	usgsugaaUfgUfCfUfaaa uaguguaL96	622	VPusAfscauu(Agn)uau agaCfaUfucacasgsa	710	UCUGUGAAUGUCU AUUAGUGUA	798
AD-536233.1	uscscacaGfaAfAfCfcuu guuuuaaL96	623	VPusUfsaaaa(Cgn)agg guuUfcUfguggasgsc	711	GCUCCACAGAAACC CUGUUUUUAU	799
AD-538141.1	gsasuucAfaCfCfAfcuu uugcuuaL96	624	VPusUfsagca(Agn)aug uggUfuGfaaacsasu	712	AUGAUUUCACCA CAUUGCUAG	800
AD-538622.1	ususcuguCfuGfUfGfaau gucuaaL96	625	VPusAfsuaga(Cgn)uuu cacAfgAfcagaasasg	713	CUUUCUGUCUGUG AAUGUCUUAU	801
AD-537580.1	uscsgguUfuGfGfGfuac aguuaaaL96	626	VPusUfsuaac(Tgn)gua cccAfaAfcagagasg	714	CUUCUGGUUUGGG UACAGUUAAA	802
AD-536505.1	csasuacuGfaGfGfGfuga aauuuaaL96	627	VPusUfsuaau(Tgn)uca cccUfcAfguagsgsa	715	UCCAUAUGAGGG UGAAAUUAAG	803
AD-537918.1	gsgscagCfuGfGfCfuug ugaucuaL96	628	VPusAfsagau(Cgn)caa gccAfgCfugccsusu	716	AAGGCACGUGGC UUGUGAUCUU	804
AD-537913.1	gsasaagGfcAfCfGfcug gcuuguaL96	629	VPusAfscaag(Cgn)cag cguGfcCfuuuucsasa	717	UUGAAAAGGCACG CUGGCUUGUG	805
AD-538642.1	usasuguAfuUfGfUfgu guuuuaaL96	630	VPusUfsuaaa(Agn)cac acaAfuAfcuacuasusa	718	UAUAGUGUAUUGU GUGUUUUAAC	806
AD-536877.1	usgsaacaUfaUfAfcfaaa gauguuaL96	631	VPusAfsacau(Cgn)uau guaUfaUfguucasgsc	719	GCUGAACAUUAC AUAGAUGUUG	807

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-538650.1	usgsugugUfuUfUfAfaca aaugauaL96	632	VPusAfsucau(Tgn)ugu uaaAfaCfacacasasu	720	AUUGUGUGUUUUA ACAAAUGAUU	808
AD-538625.1	usgsucugUfgAfAfUfguc uauauaaL96	633	VPusUfsauau(Agn)gac auuCfaCfagacagsa	721	UCUGUCUGUGAAU GUCUAUAUAG	809
AD-537911.1	usugaaaAfgGfCfAfcgc uggcuuaL96	634	VPusAfsagcc(Agn)gcg ugcCfuUfuucaasusu	722	AAUUGAAAAGGCA CGCUGGCUUG	810
AD-538014.1	usgsacucAfcUfUfUfauc aaugauaL96	635	VPusAfsucau(Tgn)gau aaaGfuGfagucagsc	723	GCUGACUCACUUU AUCAAUAGUU	811
AD-538634.1	asusgucuAfuAfUfAfgug uauuguaL96	636	VPusAfscaau(Agn)cac uauAfuAfgacaususc	724	GAAUGUCUAUAUA GUGUAUUGUG	812
AD-536979.1	gsusaaagAfgGfUfUfucu aaccuaaL96	637	VPusUfsggu(Tgn)aga aacCfuCfuuaacsasa	725	UUGUAAAAGAGGUU UCUAACCCAC	813
AD-538641.1	asusagugUfaUfUfGfugu guuuuaaL96	638	VPusUfsaaaa(Cgn)aca caaUfaCfacuaasasu	726	AUAUAGUGUAUUG UGUGUUUUA	814
AD-537912.1	usgsaaaaGfgCfAfCfugu ggcuugaL96	639	VPusCfsaagc(Cgn)agc gugCfcUfuucasasu	727	AUUGAAAAGGCAC GCUGGCUUGU	815
AD-537761.1	csuscauuAfcUfGfCfcaa caguuaaL96	640	VPusAfsaacu(Ggn)uu ggcaGfuAfaugagsgsg	728	CCCUCAUACUGCC AACAGUUUC	816
AD-537917.1	asgsacacGfcUfGfGfcuu gugaucL96	641	VPusGfsauca(Cgn)aag ccaGfcGfugccususu	729	AAAGGCACGCUGG CUUGUGAUCU	817
AD-537916.1	asasggcaCfcUfUfGfugu ugugauaL96	642	VPusAfsucau(Agn)agc cagCfUfgccususu	730	AAAAGGCACGCUG GCUUGUGAUC	818
AD-538432.1	gsasucacCfuGfCfGfugu cccaucaL96	643	VPusGfsaugg(Ggn)aca cgcAfgGfugaucsasc	731	GUGAUCACCUGCG UGUCCCAUCU	819
AD-538529.1	csusacacUfcCfUfAfaua gacuuaaL96	644	VPusUfsaagu(Cgn)uau uagGfaGfugagsgsc	732	GCCUCACCUCCUAA UAGACUUAG	820
AD-537867.1	csasgguuAfaGfAfUfcuu gguuuaaL96	645	VPusUfsaaac(Cgn)aug aucUfuAfggcugsgsc	733	GCCAGCCUAGAUAUC AUGGUUUAG	821
AD-536503.1	uscscuuuAfuGfAfGfggu gaaauuaL96	646	VPusAfsauuu(Cgn)acc cucAfgUfauggasgsu	734	ACUCCAUAACUGAG GGUGAAAUUA	822
AD-537582.1	usgsuuuuGfgGfUfAfcag uuuaaL96	647	VPusCfsuuuu(Agn)cu guacCfcAfaaccasgsa	735	UCUGGUUUUGGGUA CAGUUAAGG	823
AD-537915.1	asasaggeAfcGfCfUfggc uugugaaL96	648	VPusUfscaca(Agn)gcc agcGfuGfcccususc	736	GAAAAGGCACGCU GGCUUGUGAU	824
AD-537919.1	gscsacgcUfgGfCfUfugu gaucuaaL96	649	VPusAfsagau(Cgn)aca agcCfaGfugcscsu	737	AGGCACGCUGGCU UGUGAUCUUA	825
AD-537581.1	csusgguuUfgGfGfUfaca guuaaaaL96	650	VPusUfsuuuu(Cgn)ug uaccCfaAfaccagsasa	738	UUCUGGUUUUGGGU ACAGUUAAG	826
AD-538483.1	ususcucuUfcAfGfCfuuu gaaaaaL96	651	VPusCfsuuuu(Cgn)aaa gcuGfaAfgagaasasu	739	AUUUCUCUUCAGC UUUGAAAAGG	827

Table 8. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 3

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-523561.1	asgscucgCfaUfGfGfucaguaaaaaL96	1014	VPusUfsuuuAfcUfGfaccUfgCfagcuscusg	1107	CAAGCUCGCAUGGU CAGUAAAAG	1200
AD-523565.1	csgscaugGfuCfAfGfuaaaagcaaaL96	1015	VPusUfsugcUfuUfUfucugAfcCfaugcgsasg	1108	CUCGCAUGGUCAGU AAAAGCAAA	1201
AD-523562.1	gscsucgcAfuGfGfUfcaguaaaagaL96	1016	VPusCfsuuuUfaCfUfgaccAfuGfcgagcsusu	1109	AAGCUCGCAUGGUC AGUAAAAGC	1202
AD-526914.1	ususgcaaGfuCfCfCfaugauuucuaL96	1017	VPusAfsгааAfuCfAfu gggAfcUfugcaasgsu	1110	ACUUGCAAGUCCCA UGAUUUCUU	1203
AD-526394.1	gsascucaCfuUfUfAf ucaauaguuaL96	1018	VPusAfsacuAfuUfGfa uaaAfgUfgagucsasg	1111	CUGACUCACUUUAU CAAUAGUUC	1204
AD-395452.1	asasaggaCfGfCfAfUfg uaucuugaaL96	1019	VPusUfscaaGfaUfAfca ugCfGfUfcuuususu	1112	AAAAAGGACGCAUG UAUCUUGAA	1205
AD-525343.1	uscsuugaAfaUfGfCf uuguaaagaaL96	1020	VPusUfscuuUfaCfAfag caUfuUfcaagasusa	1113	UAUCUUGAAUGCU UGUAAAAGAG	1206
AD-524274.1	csasggcaAfuUfCfCfu uuugauucaL96	1021	VPusGfsaauCfaAfAfag gaAfuUfgccugsasg	1114	CUCAGGCAAUCCCU UUUGAUUCU	1207
AD-526956.1	gsasgggaCfaUfGfAf aaucaucuuaL96	1022	VPusAfsagaUfgAfUfu ucaUfgUfcccuscsc	1115	GGGAGGGACAUGA AAUCAUCUUA	1208
AD-526986.1	uscsugucUfgUfGfAf augucuuaaaL96	1023	VPusUfsauaGfaCfAfuu caCfaGfacagasa	1116	UUUCUGUCUGUGAA UGUCUAUAU	1209
AD-526296.1	gscsacgcUfgGfCfUf ugugaucuuaL96	1024	VPusAfsagaUfcAfCfaa gcCfaGfcgugcsusu	1117	AGGCACGCGGCUU GUGAUCUUA	1210
AD-526988.1	usgsucugUfgAfAfUf gucuauuaaaL96	1025	VPusUfsauaUfaGfAfca uuCfaCfagacagsa	1118	UCUGUCUGUGAAUG UCUAUAUAG	1211
AD-526957.1	asgsggacAfuGfAfAf aucaucuuaaL96	1026	VPusUfsaaGfuGfAfu uucAfuGfuccuscsc	1119	GGAGGGACAUGAA AUCAUCUUA	1212
AD-526993.1	gsusgaauGfuCfUfAf uauaguuaaL96	1027	VPusUfsacaCfuAfUfau agAfcAfuucacsasg	1120	CUGUGAAUGUCUAU AUAGUGUAU	1213
AD-527013.1	usgsugugUfuUfUfAf acaaugauaL96	1028	VPusAfsucaUfuUfGfu uaaAfaCfacacasasu	1121	AUUGUGUGUUUUA ACAAAUGAUU	1214
AD-526936.1	gscsaaguCfcCfAfUfg auuucuuaL96	1029	VPusGfsaaGfaAfUfca ugGfgAfcuugcsasa	1122	UUGCAAGUCCCAUG AUUUCUUCG	1215
AD-395453.1	asasggacGfcAfUfGf uaucuugaaaL96	1030	VPusUfsucaAfgAfUfac auGfcGfuccuususu	1123	AAAAGGACGCAUGU AUCUUGAAA	1216
AD-526989.1	gsuscuguGfaUfGfGf ucuauauagaL96	1031	VPusCfsuauAfuAfGfac auUfcAfcagacsasg	1124	CUGUCUGUGAAUGU CUAUAUAGU	1217
AD-524719.1	csusaaccAfgUfUfCfu cuuuguaaaL96	1032	VPusUfsuacAfaAfGfag aaCfuGfguuagscsc	1125	GGCUAACCAGUUCU CUUUGUAAG	1218
AD-526423.1	gsascuguAfuCfCfUf guuugcuuaaL96	1033	VPusAfsuagCfaAfAfca ggAfuAfcagucsusc	1126	GAGACUGUAUCCUG UUUGCUAUU	1219
AD-527010.1	usasuuguGfuGfUfUf uuaacaaauaL96	1034	VPusAfsuuuGfuUfAfa aacAfcAfcuaascsa	1127	UGUAUUGUGUGUU UUAACAAUG	1220
AD-525305.1	gsusaggaUfuUfGfUf cuguuuuagaL96	1035	VPusCfsauaAfaCfAfga caAfaUfcacacsusa	1128	UAGUUGGAUUUGU CUGUUUAUGC	1221
AD-526987.1	csusgucuGfuGfAfAf ugucuauuaaL96	1036	VPusAfsuauAfgAfCfa uucAfcAfcagacsasa	1129	UUCUGUCUGUGAAU GUCUAUAUA	1222
AD-524331.1	gscsagcaAfcAfAfAf ggauuugaaaL96	1037	VPusUfsucaAfaUfCfu uuGfuUfgcugcsesa	1130	UGGCAGCAACAAAG GAUUUGAAA	1223
AD-525266.1	gsasgcagCfuGfAfAf cauuuacauaL96	1038	VPusAfsuguAfuAfUfg uucAfgCfugcscsa	1131	UGGAGCAGCUGAAC AUAUACAUA	1224
AD-525342.1	asuscugAfaAfUfGf cuuuguaaagaL96	1039	VPusCfsuuuAfcAfAfg cauUfuCfaagausasc	1132	GUAUCUUGAAAUGC UUGUAAAGA	1225

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-526995.1	gsasauguCfuAfUfAf uaguguauuaL96	1040	VPusAfsauaCfaCfUfau auAfgAfcuucsasc	1133	GUGAAUGUCUAUA UAGUGUAUUG	1226
AD-526298.1	ascsgcugGfcUfUfGf ugauuuuaaL96	1041	VPusUfsuaaGfaUfCfac aaGfcCfagcgusgsc	1134	GCACGCUGGCUUGU GAUCUUAUA	1227
AD-524718.1	gscsuuacCfaGfUfUfc uuuuuuaaL96	1042	VPusUfsacaAfaGfAfga acUfgGfuuagcscsc	1135	GGGCUAACAGUUC UCUUUGUAA	1228
AD-526392.1	csusgacuCfaCfUfUfu aucaauagaL96	1043	VPusCfsuauUfgAfUfaa agUfgAfgucagscsa	1136	UGCUGACUCACUUU AUCAAUAGU	1229
AD-526985.1	ususcuguCfuGfUfGf aaugucuuaL96	1044	VPusAfsuagAfcAfUfu cacAfgAfcagaasasg	1137	CUUUCUGUCUGUGA AUGUCUAUA	1230
AD-527011.1	asusugugUfgUfUfUf uaacaaugaL96	1045	VPusCfsauuUfgUfUfaa aaCfaCfacaasasc	1138	GUAUUGUGUGUUU UAACAAUGA	1231
AD-525341.1	usasucuuGfaAfUfUf gcuuguuaaL96	1046	VPusUfsuuuAfaAfGfca uuUfcAfgauagscsa	1139	UGUAUCUUGAAAU GCUUGUAAAAG	1232
AD-525265.1	gsgsagcaGfcUfGfAf acauauacaaL96	1047	VPusUfsguaUfaUfGfu ucaGfcUfgucacsasg	1140	CUGGAGCAGCUGAA CAUAUACAU	1233
AD-527004.1	asusagugUfaUfUfGf uguguuuuaaL96	1048	VPusUfsaaaAfcAfCfac aaUfaCfacaasasu	1141	AUAUAGUGUAUUG UGUGUUUUA	1234
AD-525336.1	gscsauguAfuCfUfUf gaaaugcuuaL96	1049	VPusAfsagcAfuUfUfca agAfuAfcagcsgsu	1142	ACGCAUGUAUCUUG AAAUGCUUG	1235
AD-525353.1	csusuguaAfaGfAfGf guuuuuaaL96	1050	VPusGfsuuaGfaAfAfc ucUfuUfacaagscsa	1143	UGCUUGUAAAAGAG GUUUCUAACC	1236
AD-525273.1	usgsaacaUfaUfAfCfa uagauguuaL96	1051	VPusAfsacaUfcUfAfu uaUfaUfguucasgsc	1144	GCUGAACAUUAACA UAGAUGUUG	1237
AD-524638.1	uscscacaGfaAfAfCfc cuguuuuaaL96	1052	VPusUfsaaaAfcAfGfgg uuUfcUfgugcagsgsc	1145	GCUCCACAGAAACC CUGUUUUUAU	1238
AD-526350.1	gsgscuagAfuGfGfGf auauacuguaL96	1053	VPusAfsagcUfaUfAfuc cuAfuCfuagcscsa	1146	UGGGCUAGAUAGG AUAUACUGUA	1239
AD-526962.1	csasugaaAfuCfAfUfc uuagcuuaaL96	1054	VPusUfsaagCfuAfAfga ugAfuUfucagcsusc	1147	GACAUGAAAUCAUC UUAGCUUAG	1240
AD-527005.1	usasuguaAfuUfGfUf guuuuuuaaL96	1055	VPusUfsuaaAfaCfAfc caAfuAfcacuasusa	1148	UAUAGUGUAUUGU GUGUUUUAAAC	1241
AD-525269.1	csasgcugAfaCfAfUfa uacauagaaL96	1056	VPusUfscuaUfgUfAfu augUfuCfagcugscsu	1149	AGCAGCUGAACAUU UACAUAGAU	1242
AD-524715.1	asgsggcuAfaCfAfGf guucuuuaaL96	1057	VPusAfsagaAfgAfAfc uggUfuAfgccusasa	1150	UUAGGGCUAACAG UUCUCUUUG	1243
AD-395454.1	asgsgacgCfaUfGfUfa ucuugaaaaL96	1058	VPusUfsuucAfaGfAfu acaUfgCfaguccususu	1151	AAAGGACGCAUGUA UCUUGAAAAU	1244
AD-525307.1	usgsgauuUfgUfCfUf guuuuagcuL96	1059	VPusAfsagaUfaAfAfc gaCfaAfaucacsasc	1152	GUUGGAUUUGUCU GUUUUAUGCUU	1245
AD-525352.1	gscsuuguAfaAfGfAf gguuuuuaaL96	1060	VPusUfsuagAfaAfCfcu cuUfuAfcagcsasu	1153	AUGCUUGUAAAGA GGUUUCUAAC	1246
AD-524641.1	ascsgagaAfcCfCfUfg uuuuuuuaL96	1061	VPusCfsauuAfaAfAfc ggGfuUfucugsgsg	1154	CCACAGAAACCCUG UUUUAUUGA	1247
AD-526297.1	csascgcuGfgCfUfUf gugauuuuaaL96	1062	VPusUfsaagAfuCfAfc agCfcAfgcgugscsc	1155	GGCACGCUGGCUUG UGAUCUUA	1248
AD-525268.1	gscsagcuGfaAfCfAf uauacauagaL96	1063	VPusCfsuauGfuAfUfa uguUfcAfgcugcsusc	1156	GAGCAGCUGAACAU AUACAUAGA	1249
AD-526997.1	asusgucuAfuAfUfAf guguaauuaL96	1064	VPusAfscaaUfaCfAfcu auAfuAfgacaususc	1157	GAAUGUCUAUAUA GUGUAUUGUG	1250
AD-526991.1	csusgugaAfuGfUfCf uauauagugaL96	1065	VPusCfsacuAfuAfUfag acAfuUfcacagsasc	1158	GUCUGUGAAUGUCU AUUAUAGUGU	1251
AD-527012.1	usuguguGfuUfUfUf aacaaugaaL96	1066	VPusUfscuuUfuGfUfu aaaAfcAfcacaasusa	1159	UAUUGUGUGUUUU AACAAAUGAU	1252
AD-524720.1	usasaccaGfuUfCfUfc uuuuaagaL96	1067	VPusCfsuuuAfaAfAfga gaAfcUfgguuasgsc	1160	GCUAACAGUUCUC UUUGUAAGG	1253

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-525303.1	usasguugGfaUfUfUf gucuguuuuaaL96	1068	VPusUfsaaaCfaGfAfca aaUfcCfaacuascsa	1161	UGUAGUUGGAUUU GUCUGUUUAU	1254
AD-526289.1	usgsaaaaGfgCfAfCfG cuggcuugaL96	1069	VPusCfsaagCfcAfGfcg ugCfcUfuucasasu	1162	AUUGAAAAGGCACG CUGGCUUGU	1255
AD-526992.1	usgsugaaUfgUfCfUf auauaguguaL96	1070	VPusAfscaCfaUfAfua gaCfaUfucacsgsa	1163	UCUGUGAAUGUCUA UAUAGUGUA	1256
AD-525333.1	gsascgcaUfgUfAfUf cuugaaaugaL96	1071	VPusCfsauUfcAfAfga uaCfaUfgcgucscsu	1164	AGGACGCAUGUAUC UUGAAAUGC	1257
AD-524335.1	csasacaaAfgGfAfUfu ugaaacuuaL96	1072	VPusAfsaguUfuCfAfa ucCfuUfugugscsu	1165	AGCAACAAAGGAUU UGAAACUUG	1258
AD-526990.1	uscugugAfaUfGfUf cuauauaguaL96	1073	VPusAfscaUfaUfAfga caUfuCfcagascsa	1166	UGUCUGUGAAUGUC UAUUAUGUG	1259
AD-527006.1	asgsuguaUfuGfUfGf uguuuuuacaL96	1074	VPusGfsuuAfaAfCfca acAfaUfacacusasu	1167	AUAGUGUAUUGUG UGUUUUUACA	1260
AD-526505.1	gsasuuucAfaCfCfAfc auuugcuuaL96	1075	VPusUfsagcAfaAfUfg uggUfuGfaaucsasu	1168	AUGAUUUCAACCAC AUUUGCUG	1261
AD-525309.1	ususcaccAfgAfGfUf gacuauaguaL96	1076	VPusAfsucaUfaGfUfca cuCfuGfgugaasusc	1169	GAUUCACCAGAGUG ACUAUGAUA	1262
AD-524328.1	gsusggcaGfcAfAfCf aaaggauuuuL96	1077	VPusAfsaaUfcUfUfug uuGfcUfgccacsug	1170	CAGUGGCAGCAACA AAGGAUUUG	1263
AD-395455.1	gsgsacgcAfuGfUfAf ucuugaaaauL96	1078	VPusAfsuuCfaAfGfa uacAfuGfcgucscsu	1171	AAGGACGCAUGUAU CUUGAAAUA	1264
AD-526428.1	usasuccuGfuUfUfGf cuauugcuuaL96	1079	VPusAfsagcAfaUfAfge aaAfcAfggauascsa	1172	UGUAUCCUGUUUGC UAUUGCUG	1265
AD-526847.1	ususcucuUfcAfGfCf uuugaaaagaL96	1080	VPusCfsuuUfcAfAfa gcuGfaAfgagaasasu	1173	AUUUCUCUUCAGCU UUGAAAAGG	1266
AD-525957.1	uscugguUfuGfGfGf uacaguuaaaL96	1081	VPusUfsuaCfuGfUfca ccAfaAfcagascsg	1174	CUUCUGGUUUGGGU ACAGUUAAG	1267
AD-524332.1	csasgcaaCfaAfAfGfg auuugaaaaL96	1082	VPusUfsuucAfaAfUfcc uuUfgUfugcugscsc	1175	GGCAGCAACAAAGG AUUUGAAAC	1268
AD-526291.1	asasaaggCfaCfGfCfu ggcuugugaL96	1083	VPusCfsacaAfgCfCfag cgUfgCfuuuusesa	1176	UGAAAAGGCACGCU GGCUUGUGA	1269
AD-526485.1	usgscucGfuAfAfCf ccuuuucuaL96	1084	VPusAfsugaAfaAfGfg guuAfcGfaggcasgsu	1177	ACUGCCUCGUAACC CUUUUCAUG	1270
AD-526292.1	asasagcAfcGfCfUfg gcuugugaalL96	1085	VPusUfscacAfaGfCfca gcGfuGfccuuususc	1178	GAAAAGGCACGCUG GCUUGUGAU	1271
AD-524642.1	csasgaaaCfcCfUfGfu uuuauugaaL96	1086	VPusUfscaaUfaAfAfca agGfgUfuucugsusg	1179	CACAGAAACCCUGU UUUAUUGAG	1272
AD-526290.1	gsasaaagGfcAfCfGfc uggcuuguaL96	1087	VPusAfscaaGfcCfAfge guGfcCfuuuucsasa	1180	UUGAAAAGGCACGC UGGCUUGUG	1273
AD-525959.1	usgsuuuGfgGfUfAf caguuaaagaL96	1088	VPusCfsuuAfaCfUfg uacCfcAfaaccasgsa	1181	UCUGGUUUGGGUAC AGUUAAGG	1274
AD-526293.1	asasggcaCfGfUfGfg cuuguguaL96	1089	VPusAfsucaCfaAfGfcc agCfGfugccuususu	1182	AAAAGGCACGCUGG CUUGUGAUC	1275
AD-524899.1	csasuacuGfaGfGfGf ugaaauuaaaL96	1090	VPusUfsuaUfuUfCfca ccUfcAfguagsgsa	1183	UCCAUACUGAGGGU GAAAUUAAG	1276
AD-526391.1	gscsugacUfcAfCfUf uuaucaauaaL96	1091	VPusUfsauGfaUfAfaa guGfaGfucacsasg	1184	CUGCUGACUCACU UAUCAUAG	1277
AD-525956.1	ususcuggUfuUfGfGf guacaguuaaL96	1092	VPusUfsaacUfgUfAfcc caAfaCfcagaaasgsu	1185	ACUUCUGGUUUGGG UACAGUUA	1278
AD-525958.1	csusgguUfgGfGfUf acaguuaaaaL96	1093	VPusUfsuuaAfcUfGfu accCfaAfacagsasa	1186	UUCUGGUUUGGGU ACAGUUAAG	1279
AD-526351.1	gscsuagaUfaGfGfAf uauacuguaaL96	1094	VPusUfsacaGfuAfUfau ccUfaUfcuagcsesc	1187	GGGCUAGAUAGGA UAUACUGUAU	1280
AD-526138.1	csuscauuAfcUfGfCfc aacaguuaaL96	1095	VPusAfsaacUfgUfUfg gcaGfuAfaugagsgsg	1188	CCCUCAUUACUGCC AACAGUUUC	1281

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-524898.1	cscsauacUfgAfGfGf gugaaauuaaL96	1096	VPusUfsaaUfuCfAfcc cuCfaGfuauugsasg	1189	CUCCAUACUGAGGG UGAAAUUAA	1282
AD-526244.1	csasgccuAfaGfAfUfc augguuuuaaL96	1097	VPusUfsaaaCfcAfUfga ucUfuAfggcugsgsc	1190	GCCAGCCUAAGAUC AUGGUUUAG	1283
AD-525359.1	asasgaggUfuUfCfUf aaccacccaL96	1098	VPusGfsgguGfgGfUfu agaAfaCfcucuususa	1191	UAAAGAGGUUUCU AACCCACCCU	1284
AD-526393.1	usgsacucAfcUfUfUf aucaauaguaL96	1099	VPusAfscaaUfuGfAfua aaaGfuGfagucasgsc	1192	GCUGACUCACUUUA UCAAUAGUU	1285
AD-525355.1	usgsuaaaGfaGfGfUf uucuaacccaL96	1100	VPusGfsgguUfaGfAfa accUfcUfuucasasg	1193	CUUGUAAAAGAGGU UUCUAACCCA	1286
AD-526288.1	usugaaaAfgGfCfAf cgcuggcuaaL96	1101	VPusAfsagcCfaGfCfGu gcCfuUfucaasusu	1194	AAUUGAAAAGGCAC GCUGGCUUG	1287
AD-524897.1	uscscuaaCfuGfAfGf ggugaaauuaL96	1102	VPusAfsauuUfcAfCfcc ucAfgUfauggasgu	1195	ACUCCAUACUGAGG GUGAAAUUA	1288
AD-526796.1	gsasucacCfuGfCfGfu guccecauL96	1103	VPusGfsaugGfgAfCfag gcAfgGfugaucasac	1196	GUGAUCACCGUCGU GUCCCAUCU	1289
AD-526295.1	gsgscacgCfuGfGfCf uugugaucuaL96	1104	VPusAfsgauCfaCfAfag ccAfgCfugccesusu	1197	AAGGCACGCGUGCU UGUGAUCUU	1290
AD-526294.1	asgsgcacGfcUfGfGfc uugugaucaL96	1105	VPusGfsaucAfcAfAfgc caGfcGfugccesusu	1198	AAAGGCACGCGUGGC UUGUGAUCU	1291
AD-525356.1	gsusaaagAfgGfUfUf ucuaacccaL96	1106	VPusUfsgguUfuAfGfa aacCfuCfuuuacsasa	1199	UUGUAAAAGAGGU UCUAACCCAC	1292

Table 9. MAPT Single Dose Screens in BE(2)C Cells-Screen 1

Duplex	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-523799.1	17.36	3.97	11.83	1.28	17.00	3.42	33.86	5.82
AD-523802.1	24.65	6.12	14.26	4.22	17.60	1.38	37.77	4.80
AD-523795.1	15.06	1.14	14.32	4.31	19.43	2.63	49.55	5.88
AD-523810.1	22.03	2.01	15.54	0.42	24.58	3.23	66.10	9.27
AD-523809.1	22.64	1.86	16.37	1.29	22.27	1.48	51.72	4.70
AD-1019331.1	22.45	6.03	17.14	2.18	18.12	5.03	46.43	8.15
AD-523801.1	30.34	5.46	17.25	1.28	23.02	0.44	50.53	3.94
AD-523823.1	32.84	3.33	17.73	1.68	30.11	4.13	52.21	5.32
AD-523798.1	20.68	2.76	17.96	1.61	21.10	2.03	38.97	3.21
AD-523816.1	24.91	6.18	18.77	1.88	29.33	5.29	54.12	7.24
AD-523824.1	34.17	4.53	18.89	1.66	27.31	3.46	60.77	7.82
AD-523800.1	27.52	5.67	19.43	2.27	27.63	3.56	60.07	5.86
AD-523796.1	19.03	6.36	20.64	3.71	21.27	3.35	54.11	3.40
AD-523803.1	25.88	7.39	21.13	2.70	26.60	1.32	67.90	18.26
AD-523817.1	37.63	2.85	21.47	2.78	29.58	4.88	69.18	10.99
AD-523825.1	23.52	3.91	22.27	6.00	30.65	8.26	69.55	14.02
AD-523811.1	23.44	3.46	23.39	1.57	31.07	4.77	80.50	9.46
AD-523854.1	38.58	6.09	23.51	4.93	41.01	4.24	82.38	10.53

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-523797.1	34.14	5.08	25.19	1.67	31.86	1.84	66.73	4.15
AD-523805.1	39.86	2.59	25.33	2.96	34.54	6.80	72.34	9.00
AD-523814.1	31.62	5.51	25.33	3.91	38.60	1.56	66.76	9.04
AD-523804.1	34.84	5.59	25.45	1.55	32.22	6.74	68.98	4.43
AD-1019356.1	30.49	5.19	25.70	1.16	37.22	3.05	83.40	4.07
AD-523846.1	29.77	3.31	25.92	2.07	41.48	6.52	82.33	5.66
AD-523808.1	41.79	5.30	26.76	2.40	33.67	3.71	74.54	4.14
AD-523835.1	30.93	7.93	26.84	2.16	39.37	2.31	62.21	4.90
AD-1019357.1	36.22	1.99	26.90	3.71	37.60	3.98	76.42	5.26
AD-523853.1	27.78	6.30	28.49	4.67	43.46	5.81	88.34	9.82
AD-523819.1	N/A	N/A	28.54	3.64	42.29	7.21	93.19	4.81
AD-523830.1	34.94	3.25	29.70	1.93	46.68	9.09	84.11	14.32
AD-523834.1	31.77	2.15	29.97	0.78	50.66	10.05	79.85	15.25
AD-523850.1	35.59	7.65	30.23	0.56	32.27	2.34	72.88	4.06
AD-523820.1	41.60	4.75	30.69	3.92	63.61	3.48	86.22	4.77
AD-523849.1	36.88	6.27	30.74	9.03	65.52	11.32	117.05	8.49
AD-523845.1	41.26	4.71	31.05	3.90	52.35	9.41	87.04	13.11
AD-393758.3	102.71	7.60	31.14	9.50	48.85	7.58	94.84	5.35
AD-523848.1	38.58	0.98	31.32	4.94	30.21	6.74	82.58	19.58
AD-523840.1	38.40	3.17	31.47	5.14	49.17	3.50	80.62	7.66
AD-523828.1	38.31	0.88	31.80	1.25	56.98	11.05	96.66	8.50
AD-523822.1	40.68	3.68	32.06	7.63	48.94	5.35	73.53	9.58
AD-523806.1	42.23	3.39	33.39	4.10	38.73	4.97	76.41	7.34
AD-523831.1	45.89	4.78	33.75	4.48	36.69	5.48	76.20	6.09
AD-393757.1	28.66	5.31	33.83	4.47	45.96	8.04	90.16	7.54
AD-523839.1	47.43	3.54	34.37	2.50	54.71	3.17	87.09	7.01
AD-523815.1	51.86	3.12	34.40	4.52	43.71	10.84	78.90	3.64
AD-523856.1	47.69	9.26	34.49	1.24	49.13	4.20	106.48	4.88
AD-1019330.1	42.05	8.45	34.61	5.05	45.07	5.15	88.42	8.85
AD-523829.1	46.44	4.53	38.58	3.44	61.47	4.02	84.88	9.60
AD-523855.1	58.26	9.58	38.87	5.19	58.64	6.76	91.31	33.98
AD-523836.1	46.88	8.29	39.08	4.02	60.37	8.65	84.60	12.08
AD-1019329.1	46.82	5.33	40.62	4.47	50.55	6.13	79.08	7.40
AD-523843.1	44.23	2.98	41.23	4.16	56.43	7.41	83.33	14.89
AD-523807.1	53.76	7.43	41.33	7.22	53.88	6.20	76.36	8.12
AD-523821.1	57.09	5.83	43.35	3.19	68.52	7.26	96.94	7.49
AD-523826.1	66.07	3.43	43.54	4.85	85.29	8.12	113.96	30.15
AD-523847.1	62.91	2.16	44.18	5.29	65.26	11.48	99.54	8.60
AD-523786.1	57.38	1.50	47.58	10.57	59.96	6.62	107.01	4.44
AD-523812.1	N/A	N/A	47.59	4.50	61.83	2.47	107.93	3.85

	50 nM Dose		10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-523827.1	62.22	4.24	48.54	3.90	74.19	9.00	114.87	3.91
AD-523844.1	60.08	3.38	50.30	5.01	75.30	8.54	84.25	8.63
AD-523851.1	60.77	13.33	53.50	4.43	74.46	6.10	112.55	11.72
AD-523818.1	57.31	6.99	53.83	6.54	69.76	6.65	101.09	12.70
AD-523832.1	54.56	8.91	56.40	7.44	79.87	12.26	122.46	16.33
AD-523813.1	86.63	8.22	65.84	5.07	74.62	9.81	86.86	8.21
AD-523841.1	70.75	1.45	71.81	17.54	100.34	11.20	126.55	3.27
AD-1019352.1	90.08	4.18	81.29	7.58	82.18	8.87	106.93	10.34
AD-1019354.1	100.85	16.07	84.77	8.38	84.08	14.32	115.08	11.91
AD-523852.1	104.45	6.49	85.75	5.16	105.39	7.11	124.46	13.53
AD-523842.1	101.86	4.42	86.70	6.16	104.06	5.91	117.32	12.82
AD-523833.1	66.80	6.03	88.60	33.58	80.46	22.83	100.71	19.71
AD-1019328.1	100.92	11.47	90.93	7.76	93.23	13.25	100.56	4.59
AD-1019355.1	89.32	13.16	99.94	15.77	90.59	5.30	95.12	3.94
AD-1019353.1	118.09	10.16	100.93	9.24	92.43	3.47	109.80	3.42
AD-1019350.1	123.59	27.60	119.47	14.52	110.74	9.75	107.58	8.73
AD-1019351.1	126.66	52.81	138.14	16.24	121.09	3.59	112.83	10.46

Table 10. MAPT Single Dose Screens in BE(2)C Cells-Screen 2

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-535094.1	35.76	3.97	46.85	7.73	73.63	8.23
AD-535095.1	47.10	5.31	57.17	5.03	84.07	8.69
AD-538647.1	48.79	1.19	51.77	5.37	69.46	5.30
AD-535922.1	49.19	4.51	58.00	3.65	66.15	4.62
AD-536317.1	52.43	6.66	67.63	16.86	76.08	4.48
AD-536911.1	52.76	7.29	73.99	19.66	60.59	12.06
AD-538626.1	52.98	4.51	67.94	7.88	87.83	11.34
AD-535864.1	53.86	1.57	53.45	4.96	58.45	7.29
AD-535925.1	54.21	16.94	55.64	7.40	67.07	14.57
AD-538012.1	54.39	5.16	68.15	11.29	80.64	10.99
AD-536872.1	56.50	3.43	63.99	5.43	74.55	7.14
AD-536954.1	57.36	6.40	67.98	5.59	64.86	5.82
AD-536964.1	57.85	7.00	63.81	9.50	78.27	9.12
AD-536318.1	58.28	5.21	74.33	10.15	74.24	3.98
AD-536976.1	58.40	5.31	69.37	6.99	77.16	8.95

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-538630.1	58.93	4.10	71.69	5.10	80.90	5.93
AD-538624.1	59.72	3.62	76.16	7.62	88.40	6.89
AD-538594.1	60.04	5.54	68.11	3.65	96.64	8.71
AD-536915.1	60.28	4.41	66.46	5.44	81.81	15.47
AD-536870.1	60.55	6.78	67.17	5.88	67.38	7.16
AD-536236.1	60.81	4.65	72.33	2.87	81.77	6.44
AD-536319.1	60.97	3.59	78.50	6.73	82.85	5.52
AD-536966.1	61.25	8.38	65.89	5.53	85.73	15.42
AD-538643.1	61.41	7.04	67.98	5.76	82.79	8.84
AD-536873.1	62.21	2.32	72.29	7.01	78.21	10.07
AD-536952.1	62.32	6.66	65.83	7.80	76.44	11.24
AD-536959.1	62.62	22.64	71.73	16.89	63.72	16.30
AD-537921.1	62.72	6.15	77.86	6.92	101.16	7.46
AD-538652.1	62.75	2.52	66.45	5.20	85.73	7.62
AD-538649.1	62.78	5.41	69.25	5.14	79.92	5.74
AD-538623.1	62.95	4.71	77.45	4.67	93.85	10.54
AD-538573.1	63.02	10.35	71.64	4.35	96.74	7.54
AD-537920.1	63.37	11.00	69.38	5.51	96.52	13.11
AD-536939.1	63.57	5.74	71.47	5.84	83.48	16.47
AD-538015.1	63.70	8.95	85.29	13.45	94.52	15.51
AD-536953.1	63.93	7.91	66.90	6.78	72.74	4.40
AD-536237.1	64.02	4.11	72.66	8.39	82.24	11.96
AD-538628.1	64.33	5.43	70.86	3.41	87.75	6.31
AD-538632.1	64.48	4.39	73.73	9.24	97.61	8.34
AD-536975.1	64.98	9.64	70.42	9.15	69.13	7.30
AD-538599.1	65.71	6.32	66.54	8.25	93.84	5.77
AD-536978.1	66.37	7.47	65.89	5.50	77.09	7.81
AD-536956.1	67.30	6.10	77.35	9.48	80.58	7.54
AD-538571.1	68.13	20.52	84.47	18.75	102.13	30.34
AD-535921.1	68.19	8.02	73.24	7.87	74.22	6.27
AD-538593.1	68.56	3.04	81.22	2.63	104.96	4.62
AD-537974.1	68.68	2.97	71.22	5.75	97.28	5.14
AD-537973.1	69.43	10.63	81.52	8.52	112.03	1.48
AD-536982.1	69.89	19.69	85.54	37.34	82.26	33.94
AD-535918.1	70.04	7.81	75.07	4.56	78.75	6.80
AD-538627.1	70.23	7.23	77.23	7.74	95.64	5.67
AD-536913.1	70.95	13.00	73.73	15.50	98.54	13.42
AD-536869.1	71.88	6.62	84.66	2.07	80.49	10.02
AD-536965.1	72.02	4.46	76.02	5.30	99.07	7.12
AD-537914.1	72.08	5.66	82.07	2.69	107.92	8.77

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-536504.1	72.23	3.63	83.85	15.57	103.03	9.41
AD-538013.1	72.37	7.91	87.46	5.78	98.39	7.19
AD-537579.1	72.49	6.16	82.27	12.01	100.88	8.48
AD-538629.1	73.44	5.16	79.31	3.85	104.68	9.84
AD-536233.1	73.57	12.33	79.27	11.10	92.54	15.86
AD-538141.1	73.58	2.10	79.05	4.13	104.80	16.39
AD-538622.1	73.71	5.63	79.32	3.90	99.78	7.36
AD-537580.1	73.92	12.56	91.82	8.93	114.56	10.74
AD-536505.1	76.21	3.52	91.14	8.18	102.96	13.26
AD-537918.1	76.41	5.11	82.87	15.29	101.61	13.29
AD-537913.1	76.78	6.94	89.67	10.98	116.55	13.66
AD-538642.1	76.78	10.38	78.85	1.90	94.35	11.27
AD-536877.1	77.42	6.51	89.31	13.19	90.03	16.22
AD-538650.1	77.44	7.13	82.05	11.20	103.07	6.80
AD-538625.1	77.58	29.08	92.50	30.50	105.00	26.42
AD-537911.1	78.19	6.04	84.02	5.02	102.26	10.54
AD-538014.1	78.92	8.65	91.67	10.62	103.65	7.94
AD-538634.1	79.38	5.33	92.21	11.29	102.96	11.07
AD-536979.1	80.06	7.58	83.89	9.75	83.49	9.04
AD-538641.1	82.10	16.21	108.21	33.90	106.27	20.95
AD-537912.1	82.11	8.49	90.65	7.62	117.90	9.60
AD-537761.1	82.92	9.96	89.07	9.42	96.90	3.72
AD-537917.1	83.41	6.99	93.61	12.88	94.23	7.10
AD-537916.1	83.48	8.36	93.61	6.79	100.30	3.39
AD-538432.1	84.04	12.10	88.02	4.69	118.69	12.50
AD-538529.1	86.01	6.49	100.18	3.64	110.99	17.88
AD-537867.1	86.51	7.59	104.38	17.22	98.08	7.46
AD-536503.1	89.05	17.95	96.08	13.91	80.32	18.37
AD-537582.1	89.85	4.17	114.48	4.03	110.08	14.89
AD-537915.1	90.25	14.83	109.37	7.19	128.31	18.33
AD-537919.1	91.79	17.57	102.61	16.28	118.80	34.98
AD-537581.1	94.66	8.07	98.82	12.41	116.58	8.07
AD-538483.1	100.69	3.19	110.69	9.92	104.44	11.39

Table 11. MAPT Single Dose Screens in BE(2)C Cells-Screen 3

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-523561.1	24.25	4.75	41.99	4.98	82.19	23.42
AD-523565.1	27.04	2.31	38.72	1.37	64.07	18.18
AD-523562.1	31.34	4.59	63.36	2.89	79.88	8.60
AD-526914.1	51.27	5.89	68.78	8.49	73.60	10.78
AD-526394.1	51.80	4.57	68.62	7.93	85.80	13.09
AD-395452.1	52.02	6.28	70.03	2.56	71.84	2.62
AD-525343.1	53.14	2.47	73.00	9.09	65.65	5.26
AD-524274.1	53.18	11.25	73.03	13.76	74.86	16.82
AD-526956.1	55.49	2.40	69.19	3.74	83.47	5.73
AD-526986.1	55.75	12.71	67.26	6.74	82.19	5.91
AD-526296.1	57.10	7.67	62.13	1.83	88.80	5.26
AD-526988.1	57.17	4.10	68.30	1.72	70.09	2.53
AD-526957.1	57.35	2.66	71.03	6.52	83.66	8.91
AD-526993.1	57.49	2.34	73.71	10.34	74.47	7.49
AD-527013.1	59.03	9.70	78.09	9.74	83.15	9.66
AD-526936.1	59.58	2.95	76.70	5.34	82.47	1.93
AD-395453.1	59.92	9.75	76.90	5.81	79.27	1.57
AD-526989.1	60.47	8.42	79.80	9.09	79.67	9.60
AD-524719.1	60.48	1.36	76.63	2.48	95.71	6.15
AD-526423.1	60.79	7.37	71.34	2.60	80.78	2.42
AD-527010.1	60.86	8.24	71.48	7.52	76.33	6.19
AD-525305.1	61.31	9.29	101.55	49.60	71.50	3.58
AD-526987.1	61.65	7.18	101.29	40.95	93.55	14.50
AD-524331.1	61.89	7.55	69.03	4.56	96.90	9.09
AD-525266.1	62.38	0.43	81.15	9.74	78.98	10.39
AD-525342.1	62.96	2.46	73.61	4.98	67.30	3.67
AD-526995.1	63.38	5.58	73.78	4.08	79.53	10.96
AD-526298.1	63.43	9.00	61.85	5.32	89.31	8.65
AD-524718.1	63.50	2.14	92.54	9.33	105.11	6.99
AD-526392.1	63.79	9.35	65.84	9.52	75.66	3.01
AD-526985.1	63.91	14.65	76.32	2.35	78.06	6.17
AD-527011.1	64.03	3.23	78.11	8.73	78.45	5.83
AD-525341.1	64.23	5.92	72.27	5.91	67.06	7.45
AD-525265.1	64.79	6.18	75.73	10.69	87.89	9.59
AD-527004.1	64.82	7.28	63.29	4.61	76.33	3.53
AD-525336.1	64.83	11.12	80.03	20.95	67.48	5.03
AD-525353.1	64.90	5.94	85.77	10.42	91.67	11.10
AD-525273.1	65.56	5.72	78.29	12.90	78.31	19.70

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-524638.1	65.61	1.80	92.33	21.29	90.73	7.19
AD-526350.1	65.71	6.19	63.29	4.00	87.15	5.74
AD-526962.1	65.96	10.41	75.90	7.41	89.12	5.59
AD-527005.1	65.99	4.44	64.80	10.69	75.15	6.07
AD-525269.1	66.10	2.88	83.00	6.51	69.89	10.33
AD-524715.1	66.47	3.71	84.61	15.13	89.26	15.60
AD-395454.1	66.86	7.80	87.90	3.70	64.50	14.56
AD-525307.1	66.97	6.41	74.53	7.67	65.62	4.65
AD-525352.1	67.17	13.74	73.45	9.77	74.40	6.13
AD-524641.1	67.37	2.96	69.97	9.15	81.33	9.62
AD-526297.1	67.73	3.10	61.09	2.81	81.82	3.96
AD-525268.1	67.83	5.44	78.87	12.21	96.08	2.23
AD-526997.1	68.00	9.39	92.04	34.36	102.14	18.87
AD-526991.1	68.04	5.87	79.31	8.41	83.68	3.96
AD-527012.1	68.67	4.36	76.25	4.13	78.09	6.83
AD-524720.1	68.77	2.59	82.86	10.38	112.52	15.70
AD-525303.1	69.44	15.86	107.37	33.92	123.02	51.68
AD-526289.1	69.83	4.96	84.13	9.96	86.99	5.63
AD-526992.1	69.85	6.36	76.94	7.30	83.97	12.58
AD-525333.1	69.96	8.49	110.83	33.93	123.94	65.67
AD-524335.1	70.15	22.32	74.57	26.56	82.47	9.69
AD-526990.1	70.16	2.78	88.92	9.37	82.68	8.97
AD-527006.1	70.32	9.10	73.70	7.13	77.32	4.98
AD-526505.1	71.05	1.71	68.69	10.79	89.52	9.27
AD-525309.1	71.25	6.44	74.02	14.37	75.43	12.20
AD-524328.1	71.41	4.91	75.62	9.86	91.35	14.35
AD-395455.1	71.54	12.98	86.22	6.66	79.04	11.18
AD-526428.1	72.21	3.20	68.14	8.91	82.27	4.63
AD-526847.1	72.53	5.07	78.38	4.07	94.95	12.28
AD-525957.1	72.71	3.10	73.73	4.87	82.24	6.38
AD-524332.1	73.34	3.13	86.68	9.09	121.33	17.30
AD-526291.1	73.45	10.45	82.25	9.88	82.01	7.79
AD-526485.1	75.46	7.07	88.92	17.06	110.64	6.07
AD-526292.1	76.34	3.87	84.96	5.08	91.33	6.41
AD-524642.1	76.36	4.44	89.36	5.71	78.17	9.16
AD-526290.1	76.40	0.35	81.85	2.77	93.57	6.41
AD-525959.1	80.21	5.70	78.87	10.19	94.76	11.52
AD-526293.1	80.56	4.21	87.13	12.23	90.70	13.76
AD-524899.1	80.63	7.75	99.24	7.93	96.78	3.60
AD-526391.1	81.11	11.53	67.87	4.96	88.18	5.14

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-525956.1	81.17	12.92	82.75	4.11	76.04	7.59
AD-525958.1	81.48	5.89	97.77	16.51	86.08	9.55
AD-526351.1	81.74	7.87	80.06	6.54	83.31	5.66
AD-526138.1	82.32	1.60	78.42	13.50	86.18	3.40
AD-524898.1	83.75	11.29	133.26	47.06	89.58	15.95
AD-526244.1	85.72	8.98	81.31	12.02	88.47	4.25
AD-525359.1	88.09	37.42	79.82	4.76	78.34	2.90
AD-526393.1	90.24	27.07	77.17	13.67	83.78	12.77
AD-525355.1	91.77	20.82	95.83	12.89	91.45	4.65
AD-526288.1	93.76	43.34	71.19	8.02	94.88	12.86
AD-524897.1	96.55	23.90	129.17	45.05	96.85	22.02
AD-526796.1	104.68	6.01	94.28	11.15	105.95	5.95
AD-526295.1	107.65	29.68	103.40	23.46	98.05	19.18
AD-526294.1	112.78	6.67	99.54	7.26	89.79	6.44
AD-525356.1	129.10	42.23	111.99	33.71	82.86	5.42

Table 12. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 4

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2
AD-393758.1	AGUGUGCAAAU AGUCUACAAA	1293	NM_001038609.2 _1065- 1085_G21U_s	1065- 1085	UUUGUAGACU AUUUGCACAC UGC	1341	NM_001038609.2 _1063- 1085_C1A_as	1063- 1085
AD-393888.1	ACAGAGUCCAG UCGAAGAUUA	1294	NM_001038609.2 _1195- 1215_G21U_s	1195- 1215	UAAUCUUCGA CUGGACUCUG UCC	1342	NM_001038609.2 _1193- 1215_C1A_as	1193- 1215
AD-393759.1	GUGUGCAAAUA GUCUACAAGA	1295	NM_001038609.2 _1066- 1086_C21U_s	1066- 1086	UCUUGUAGAC UAUUUGCACA CUG	1343	NM_001038609.2 _1064- 1086_G1A_as	1064- 1086
AD-393761.1	GUGCAAAUAGU CUACAAGCCA	1296	NM_001038609.2 _1068- 1088_G21U_s	1068- 1088	UGGCUUGUAG ACUAUUUGCA CAC	1344	NM_001038609.2 _1066- 1088_C1A_as	1066- 1088
AD-393495.1	UCAGGUGAACC ACCAAAAUCA	1297	NM_001038609.2 _705- 725_C21U_s	705-725	UGAUUUUGGU GGUUCACCUG ACC	1345	NM_001038609.2 _703- 725_G1A_as	703-725
AD-393760.1	UGUGCAAAUAG UCUACAAGCA	1298	NM_001038609.2 _1067- 1087_C21U_s	1067- 1087	UGCUUGUAGA CUAUUUGCAC ACU	1346	NM_001038609.2 _1065- 1087_G1A_as	1065- 1087
AD-396425.1	UUUAUCAAUAG UUCCAUUUAA	1299	NM_001038609.2 _4520-4540_s	4520- 4540	UUAAAUGGAA CUAUUGAUAA AGU	1347	NM_001038609.2 _4518- 4540_as	4518- 4540
AD-395441.1	ACCAGAGUGAC UAUGAUAGUA	1300	NM_001038609.2 _3341- 3361_G21U_s	3341- 3361	UACUAUCAUA GUCACUCUGG UGA	1348	NM_001038609.2 _3339- 3361_C1A_as	3339- 3361

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2
AD-396420.1	UUCACUUUAUC AAUAGUCCA	1301	NM_001038609.2_4515-4535_s	4515-4535	UGGAACUAUU GAUAAAGUGA AUU	1349	NM_001038609.2_4513-4535_as	4513-4535
AD-397103.1	UGUGAAUGUCC AUUAGUGUA	1302	NM_001038609.2_5284-5304_s	5284-5304	UACACUAUUAU GGACAUUCAC AGA	1350	NM_001038609.2_5282-5304_as	5282-5304
AD-397104.1	GUGAAUGUCCA UAUAGUGUAA	1303	NM_001038609.2_5285-5305_s	5285-5305	UUACACUAUA UGGACAUUCA CAG	1351	NM_001038609.2_5283-5305_as	5283-5305
AD-393239.1	CGAUGCUAAGA GCACUCCAAA	1304	NM_001038609.2_344-364_C21U_s	344-364	UUUGGAGUGC UCUUAGCAUC GGA	1352	NM_001038609.2_342-364_G1A_as	342-364
AD-397102.1	CUGUGAAUGUC CAUUAAGUGA	1305	NM_001038609.2_5283-5303_s	5283-5303	UCACUAUAUG GACAUUCACA GAC	1353	NM_001038609.2_5281-5303_as	5281-5303
AD-397167.1	UGGAAUAAAG UUUUUACUCA	1306	NM_001038609.2_5354-5374_s	5354-5374	UGAGUAAUAA CUUUUUUCC AAA	1354	NM_001038609.2_5352-5374_as	5352-5374
AD-394791.1	UGGGACUUUAG GGCUAACCAA	1307	NM_001038609.2_2459-2479_G21U_s	2459-2479	UUGGUUAGCC CUAAAGUCCC AGG	1355	NM_001038609.2_2457-2479_C1A_as	2457-2479
AD-393754.1	AGGCAGUGUGC AAAUAGUCUA	1308	NM_001038609.2_1061-1081_s	1061-1081	UAGACUAUUU GCACACUGCC UCC	1356	NM_001038609.2_1059-1081_as	1059-1081
AD-393496.1	CAGGUGAACCA CCAAAUCCA	1309	NM_001038609.2_706-726_G21U_s	706-726	UGGAUUUUGG UGGUUCACCU GAC	1357	NM_001038609.2_704-726_C1A_as	704-726
AD-393667.1	AAGGUGCAGAU AAUUAUAAA	1310	NM_001038609.2_972-992_G21U_s	972-992	UUUAUUAAU AUCUGCACCU UGC	1358	NM_001038609.2_970-992_C1A_as	970-992
AD-396467.1	AUCCCAUUUGA GAUUGCUUGA	1311	NM_001038609.2_4564-4584_C21U_s	4564-4584	UCAAGCAAUC UCAAAUGGGA UAC	1359	NM_001038609.2_4562-4584_G1A_as	4562-4584
AD-393690.1	GCUGGAUCUUA GCAACGUCCA	1312	NM_001038609.2_995-1015_s	995-1015	UGGACGUUGC UAAGAUCACG CUU	1360	NM_001038609.2_993-1015_as	993-1015
AD-396449.1	CUUCAUGAUA AGAGUGUAUA	1313	NM_001038609.2_4546-4566_C21U_s	4546-4566	UAUACACUCU UAUCAUUGAA GUC	1361	NM_001038609.2_4544-4566_G1A_as	4544-4566
AD-393663.1	UGGCAAGGUGC AGAUAAUUA	1314	NM_001038609.2_968-988_s	968-988	UUAAUUAUCU GCACCUUGCC ACC	1362	NM_001038609.2_966-988_as	966-988
AD-393820.1	AGGGAACAUC AUCACAAGCA	1315	NM_001038609.2_1127-1147_C21U_s	1127-1147	UGCUGUGAU GGAUGUCCCC UAA	1363	NM_001038609.2_1125-1147_G1A_as	1125-1147
AD-396437.1	CAUUUAAUUG ACUUCAAUGA	1316	NM_001038609.2_4534-4554_s	4534-4554	UCAUUGAAGU CAAUUUAAU GGA	1364	NM_001038609.2_4532-4554_as	4532-4554
AD-393084.1	UCUGUCGAUUA UCAGGCUUUA	1317	NM_001038609.2_158-178_s	158-178	UAAAGCCUGA UAAUCGACAG AAG	1365	NM_001038609.2_156-178_as	156-178
AD-396401.1	CUGGUUCCUCC AAGCUCUUA	1318	NM_001038609.2_4494-4514_s	4494-4514	UUAAGAGCUU GGAGGAACCA GGC	1366	NM_001038609.2_4492-4514_as	4492-4514

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2
AD-394296.1	CCAAAUUGAUU UGUGGGCUAA	1319	NM_001038609.2 _1691-1711_s	1691-1711	UUAGCCCACA AAUCAUUUG GAA	1367	NM_001038609.2 _1689-1711_as	1689-1711
AD-395574.1	AUGUUUUGAAG GGUUUCUUCA	1320	NM_001038609.2 _3544-3564_s	3544-3564	UGAAGAAACC CUUCAAAACA UGG	1368	NM_001038609.2 _3542-3564_as	3542-3564
AD-393124.1	CGCCAGGAGUU UGACACAAUA	1321	NM_001038609.2 _198-218_G21U_s	198-218	UAUUGUGUCA AACUCCUGGC GAG	1369	NM_001038609.2 _196-218_C1A_as	196-218
AD-393674.1	AGAUAUUAAU AAGAAGCUGA	1322	NM_001038609.2 _979-999_G21U_s	979-999	UCAGCUUCUU AUUAAUUAUC UGC	1370	NM_001038609.2 _977-999_C1A_as	977-999
AD-396451.1	UCAUGAUAAAG AGUGUAUCCA	1323	NM_001038609.2 _4548-4568_C21U_s	4548-4568	UGGAUACACU CUUAUCAUUG AAG	1371	NM_001038609.2 _4546-4568_G1A_as	4546-4568
AD-396454.1	AUGAUAAAGAGU GUAUCCCAUA	1324	NM_001038609.2 _4551-4571_s	4551-4571	UAUGGGAUAC ACUCUUAUCA UUG	1372	NM_001038609.2 _4549-4571_as	4549-4571
AD-393376.1	GACAGGACAGG AAAUGACGAA	1325	NM_001038609.2 _543-563_G21U_s	543-563	UUCGUCAUUU CCUGUCCUGU CUU	1373	NM_001038609.2 _541-563_C1A_as	541-563
AD-393505.1	CACCAAAUCC GGAGAACGAA	1326	NM_001038609.2 _715-735_s	715-735	UUCGUUCUCC GGAUUUUGGU GGU	1374	NM_001038609.2 _713-735_as	713-735
AD-393375.1	AGACAGGACAG GAAAUGACGA	1327	NM_001038609.2 _542-562_s	542-562	UCGUCAUUUC CUGUCCUGUC UUU	1375	NM_001038609.2 _540-562_as	540-562
AD-393247.1	AGAGCACUCCA ACUGCUGAAA	1328	NM_001038609.2 _352-372_G21U_s	352-372	UUUCAGCAGU UGGAGUGCUC UUA	1376	NM_001038609.2 _350-372_C1A_as	350-372
AD-393257.1	AACUGCUGAAG ACGUGACUGA	1329	NM_001038609.2 _362-382_C21U_s	362-382	UCAGUCACGU CUUCAGCAGU UGG	1377	NM_001038609.2 _360-382_G1A_as	360-382
AD-396459.1	AAGAGUGUAUC CCAUUUGAGA	1330	NM_001038609.2 _4556-4576_s	4556-4576	UCUCAAAUGG GAUACACUCU UAU	1378	NM_001038609.2 _4554-4576_as	4554-4576
AD-396450.1	UUCAUGAUAA GAGUGUAUCA	1331	NM_001038609.2 _4547-4567_C21U_s	4547-4567	UGAUACACUC UUAUCAUUGA AGU	1379	NM_001038609.2 _4545-4567_G1A_as	4545-4567
AD-396445.1	UUGACUCAAU GAUAAGAGUA	1332	NM_001038609.2 _4542-4562_G21U_s	4542-4562	UACUCUUAUC AUUGAAGUCA AUU	1380	NM_001038609.2 _4540-4562_C1A_as	4540-4562
AD-396461.1	GAGUGUAUCCC AUUUGAGUAU	1333	NM_001038609.2 _4558-4578_s	4558-4578	UAUCUCAAU GGGAUACACU CUU	1381	NM_001038609.2 _4556-4578_as	4556-4578
AD-396452.1	CAAUGAUAGA GUGUAUCCCA	1334	NM_001038609.2 _4549-4569_s	4549-4569	UGGGAUACAC UCUUAUCAU GAA	1382	NM_001038609.2 _4547-4569_as	4547-4569
AD-396913.1	AUCUGUGGCUU UAUGAGCCUA	1335	NM_001038609.2 _5074-5094_s	5074-5094	UAGGCUCAUA AAGCCACAGA UCU	1383	NM_001038609.2 _5072-5094_as	5072-5094
AD-396455.1	UGAUAAAGAGUG UAUCCCAUUA	1336	NM_001038609.2 _4552-4572_s	4552-4572	UAAUGGGAUA CACUCUUAUC AUU	1384	NM_001038609.2 _4550-4572_as	4550-4572

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Source and Range	Range in NM_001038609.2
AD-396912.1	GAUCUGUGGCUUUAUGAGCCA	1337	NM_001038609.2_5073-5093_s	5073-5093	UGGCUCAUAAAGCCACAGAU CUA	1385	NM_001038609.2_5071-5093_as	5071-5093
AD-396915.1	CUGUGGCUUUAUGAGCCUUA	1338	NM_001038609.2_5076-5096_s	5076-5096	UGAAGGCUCAUAAAGCCACA GAU	1386	NM_001038609.2_5074-5096_as	5074-5096
AD-396453.1	AAUGAUAAAGAGUGUAUCCCAA	1339	NM_001038609.2_4550-4570_s	4550-4570	UUGGGAUACA CUCUUAUCAU UGA	1387	NM_001038609.2_4548-4570_as	4548-4570
AD-394991.1	CAUAUCUGGCUACACUAGA	1340	NM_001038609.2_2753-2773_G21U_s	2753-2773	UCUAGUGUAGAGCAGAUUU GCC	1388	NM_001038609.2_2751-2773_C1A_as	2751-2773

Table 13. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 4

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-393758.1	asgsugugCfaAfAfUfagucuaaaaL96	1389	VPusUfsuguAfgAfCfuaUfGfcacacusc	1437	GCAGUGUGCAAAUAGUCUACAAG	1485
AD-393888.1	ascagagUfcCfAfGfucgaagauuaL96	1390	VPusAfsaucUfuCfGfacugGfaCfucugusc	1438	GGACAGAGUCCAGUCGAAGAUUG	1486
AD-393759.1	gsusgugcAfaAfUfAfgucuaaagaL96	1391	VPusCfsuugUfaGfAfcuaUfUfgfcacacusc	1439	CAGUGUGCAAAUAGUCUACAAGC	1487
AD-393761.1	gsusgcaaAfaAfGfUfcuacaagccaL96	1392	VPusGfsgcuUfgUfAfgacuAfuUfugacasc	1440	GUGUGCAAAUAGUCUACAAGCCG	1488
AD-393495.1	uscagagUfaAfCfCfaccaaaaucaL96	1393	VPusGfsauuUfuGfGfugguUfcAfcugasc	1441	GGUCAGGUGAACCACCAAAAUCC	1489
AD-393760.1	usgsugcaAfaUfAfGfucuaaagcaL96	1394	VPusGfscuuGfuAfGfacuaUfuUfgcacasc	1442	AGUGUGCAAAUAGUCUACAAGCC	1490
AD-396425.1	usuuuacAfaUfAfGfuuccauuuuaL96	1395	VPusUfsaaaUfgGfAfacuUfuGfauaaasgsu	1443	ACUUUAUCAAUAGUCCAUAUUUA	1491
AD-395441.1	ascscagaGfuGfAfCfuaugauaguaL96	1396	VPusAfscaUfcAfUfagucAfcUfcugugsga	1444	UCACCAGAGUGACUAUGAUAGUG	1492
AD-396420.1	ususcacuUfuAfUfCfaaaguuccaL96	1397	VPusGfsgaaCfuAfUfugaUfaAfgugaasusu	1445	AAUUCACUUUAUCAAUAGUCCA	1493
AD-397103.1	usgsugaaUfgUfCfCfaaauaguguaL96	1398	VPusAfscaUfaUfAfuggaCfaUfucacsgsa	1446	UCUGUGAAUGUCCAUUAUAGUGUA	1494
AD-397104.1	gsusgaauGfuCfCfAfaaaguguaaL96	1399	VPusUfsacaCfuAfUfauggAfcAfuucacsg	1447	CUGUGAAUGUCCAUUAUAGUGUAU	1495
AD-393239.1	csgsaugcUfaAfGfAfgcacuccaaaL96	1400	VPusUfsuggAfgUfGfucuaUfaGfcaucgsgsa	1448	UCCGAUGCUAAGAGGCACUCCAAC	1496
AD-397102.1	csusgugaAfuGfUfcfcauauagugaL96	1401	VPusCfsacuAfuAfUfggacAfuUfcacagsasc	1449	GUCUGUGAAUGUCCAUAUAGUGU	1497
AD-397167.1	usgsaaaUfaAfAfGfuuuuuacucaL96	1402	VPusGfsaguAfaUfAfacuUfuUfuuccasasa	1450	UUUGGAAAUAAAGUUUUUACUCU	1498
AD-394791.1	usgsugacUfuUfAfGfggcuaccaaL96	1403	VPusUfsgguUfaGfCfccuaAfaGfuuccasgsg	1451	CCUGGGACUUUAGGGCUAACCAG	1499
AD-393754.1	asgsagcagUfgUfGfCfaaauagucuaL96	1404	VPusAfsagcUfaUfUfugcaCfaCfugcusc	1452	GGAGGCAGUGUGCAAAUAGUCUA	1500
AD-393496.1	csasggugAfaCfCfAfcacaaaaucaL96	1405	VPusGfsgauUfuUfGfuggUfuCfaccugsasc	1453	GUCAGGUGAACCACCAAAAUCCG	1501

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-393667.1	asasggugCfaGfAfUf aaauaauaaaL96	1406	VPusUfsuauUfaAfUfua ucUfgCfaccuusgsc	1454	GCAAGGUGCAGAU AAUUAUAAG	1502
AD-396467.1	asuscccaUfuUfGfAf gauugcuugaL96	1407	VPusCfsaagCfaAfUfcu caAfaUfgggasasc	1455	GUUCCCAUUUGA GAUUGCUUGC	1503
AD-393690.1	gscsuggaUfcUfUfA fgcaacguccaL96	1408	VPusGfsgacGfuUfGfcu aaGfaUfccagcsusu	1456	AAGCUGGAUCUUA GCAACGUCCA	1504
AD-396449.1	csusuccaUfgAfUfAf agaguguauaL96	1409	VPusAfsuacAfcUfCfu auCfaUfugaagsusc	1457	GACUUCAAUGAUA AGAGUGUAUC	1505
AD-393663.1	usgsgcaaGfgUfGfCf agauaauuaaL96	1410	VPusUfsaauUfaUfCfug caCfcUfugccascsc	1458	GGUGGCAAGGUGC AGAUAAUUA	1506
AD-393820.1	asgsggaaCfaUfCfCf aucacaagcaL96	1411	VPusGfscuuGfuGfAfu ggaUfgUfuccusasa	1459	UUAGGGAACAUC AUCACAAGCC	1507
AD-396437.1	csasuuuaAfaUfUfGf acuucuaugaL96	1412	VPusCfsauuGfaAfGfuc aaUfuUfaaugsasa	1460	UCCAUUUAAAUG ACUUCAAUGA	1508
AD-393084.1	uscsugucGfaUfUfA fucagguuuuL96	1413	VPusAfsaagCfcUfGfau aaUfcGfacagasag	1461	CUUCUGUCGAUUA UCAGGCUUUG	1509
AD-396401.1	csusgguuCfcUfCfCf aagcucuuaaL96	1414	VPusUfsaagAfgCfUfug gaGfgAfacagsgsc	1462	GCCUGGUUCCUCC AAGCUCUUA	1510
AD-394296.1	cscsaauUfgAfUfUf ugugggcuaaL96	1415	VPusUfsagcCfcAfCfaa auCfaAfuuggsasa	1463	UCCAAAUUGAUU UGUGGGCUAA	1511
AD-395574.1	asusguuuUfgAfAfG fgguuucuuaL96	1416	VPusGfsaagAfaAfCfcc uuCfaAfaacausgsg	1464	CCAUGUUUGAAG GGUUUCUUCU	1512
AD-393124.1	csgsccagGfaGfUfUf ugacacaauaL96	1417	VPusAfsuugUfgUfCfaa acUfcCfugcgcsasg	1465	CUCGCCAGGAGUU UGACACAAUG	1513
AD-393674.1	asgsauaaUfuAfAfUf aagaagcugaL96	1418	VPusCfsagcUfuCfUfua uuAfaUfuaucsgsc	1466	GCAGAUAAUUAU AAGAAGCUGG	1514
AD-396451.1	uscсаагAfUfAfGf faguguaucalL96	1419	VPusGfsgauAfcAfCfuc uuAfuCfaugasasg	1467	CUUCAUGAUAA AGUGUAUCC	1515
AD-396454.1	asusgaauAfgAfGfU fguauccecauL96	1420	VPusAfsuggGfaUfAfca cuCfuUfaucausug	1468	CAAUGAUAAAGAGU GUAUCCCAU	1516
AD-393376.1	gsascaggAfcAfGfGf aaugacgaaL96	1421	VPusUfscguCfaUfUfuc cuGfuCfcugcsusu	1469	AAGACAGGACAGG AAAUGACGAG	1517
AD-393505.1	csasccaaAfaUfCfCf ggagaacgaaL96	1422	VPusUfscguUfcUfCfcg gaUfuUfugugsgsu	1470	ACCACCAAAAUCC GGAGAACGAA	1518
AD-393375.1	asgsacagGfaCfAfGf gaaugacgaL96	1423	VPusCfsagcAfuUfUfcc ugUfcCfugcsusu	1471	AAAGACAGGACAG GAAAUGACGA	1519
AD-393247.1	asgsagcaCfuCfCfAf acugcugaaaL96	1424	VPusUfsucaGfcAfGfu ggAfgUfgcucusasa	1472	UAAGAGCACUCCA ACUGCUGAAG	1520
AD-393257.1	asascugcUfgAfAfGf acgugacugaL96	1425	VPusCfsaguCfaCfGfuc uuCfaGfcaguusgsg	1473	CCAACUGCUGAAG ACGUGACUGC	1521
AD-396459.1	asasgaguGfuAfUfCf ccauuugagaL96	1426	VPusCfsucaAfaUfGfgg auAfcAfcucusasu	1474	AUAAGAGUGUAUC CCAUUUGAGA	1522
AD-396450.1	ususcaauGfaUfAfAf gaguguaucalL96	1427	VPusGfsauaCfaCfUfcu uaUfcAfuugaasgsu	1475	ACUUCAAUGAUAA GAGUGUAUCC	1523
AD-396445.1	ususgacuUfcAfAfU fgauaagaguaL96	1428	VPusAfsucUfuAfUfca uuGfaAfgucaasusu	1476	AAUUGACUCAAU GAUAAGAGUG	1524
AD-396461.1	gsasguguAfuCfCfCf auuugagauaL96	1429	VPusAfsucuCfaAfAfug ggAfuAfcacucsusu	1477	AAGAGUGUAUCCC AUUUGAGAUU	1525
AD-396452.1	csasaugaUfaAfGfAf guguauccecaL96	1430	VPusGfsggaUfaCfAfcu cuUfaUfcauugsasa	1478	UUCAAUGAUAA GUGUAUCCCA	1526
AD-396913.1	asuscuguGfgCfUfU fuaugagccuaL96	1431	VPusAfsggcUfcAfUfaa agCfcAfcagauscsu	1479	AGAUCUGUGGCUU UAUGAGCCUU	1527
AD-396455.1	usgsauaaGfaGfUfGf uauccecauaL96	1432	VPusAfsaugGfgAfUfac acUfcUfuaucasusu	1480	AAUGAUAAAGAGUG UAUCCCAUUU	1528
AD-396912.1	gsasucugUfgGfCfU fuuaugagccalL96	1433	VPusGfsgcuCfaUfAfaa gcCfaCfagaucsusa	1481	UAGAUCUGUGGCU UUAUGAGCCU	1529

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-396915.1	csusguggCfuUfUfA fugagccuucal96	1434	VPusGfsaagGfcUfCfau aaAfgCfcacagsasu	1482	AUCUGUGGCCUUUA UGAGCCUUCA	1530
AD-396453.1	asasugauAfaGfAfGf uguaucccaal96	1435	VPusUfsgggAfuAfCfac ucUfuAfucuuusgsa	1483	UCAAUGAUAAGAG UGUAUCCCAU	1531
AD-394991.1	csasauauCfuGfCfUf cuacacuagal96	1436	VPusCfsuagUfgUfAfga gcAfgAfuaauugscsc	1484	GGCAAUAUCUGCU CUACACUAGG	1532

Table 14. MAPT Single Dose Screens in BE(2)C (human) Cells-Screen 4

Duplex	10 nM Dose		0.1 nM Dose	
	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-393758.1	4.4	1.1	41.8	7.3
AD-393888.1	6.8	0.4	50.8	4.0
AD-393759.1	8.0	1.0	43.5	6.4
AD-393761.1	14.0	2.0	72.3	13.3
AD-393495.1	14.0	1.7	33.5	7.0
AD-393760.1	19.0	2.1	67.3	3.6
AD-396425.1	24.9	4.2	40.9	7.1
AD-395441.1	26.3	6.9	39.2	7.5
AD-396420.1	30.5	6.3	41.5	7.2
AD-397103.1	40.9	6.4	55.8	7.4
AD-397104.1	41.8	8.9	62.1	4.6
AD-393239.1	42.5	7.2	74.1	5.9
AD-397102.1	44.8	4.6	59.6	4.8
AD-397167.1	45.9	12.3	53.6	5.2
AD-394791.1	47.4	10.1	78.5	4.3
AD-393754.1	50.7	3.3	81.5	20.2
AD-393496.1	51.5	4.4	85.4	10.1
AD-393667.1	54.1	12.4	78.0	6.5
AD-396467.1	58.0	9.1	90.8	7.3
AD-393690.1	58.3	3.2	78.3	13.8
AD-396449.1	60.0	10.9	82.7	11.5
AD-393663.1	61.0	12.9	76.1	9.5
AD-393820.1	61.2	10.3	93.5	11.4
AD-396437.1	64.3	7.0	80.5	9.7
AD-393084.1	68.9	9.0	92.4	4.9
AD-396401.1	70.8	7.2	94.3	3.6
AD-394296.1	77.3	5.0	93.7	7.5
AD-395574.1	77.7	11.0	80.0	6.3
AD-393124.1	78.7	18.8	97.3	3.1
AD-393674.1	79.4	15.1	82.3	11.7
AD-396451.1	79.8	11.9	102.6	7.8
AD-396454.1	87.3	4.4	99.4	5.4

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-393376.1	88.4	14.9	106.2	17.8
AD-393505.1	91.4	0.9	105.9	13.2
AD-393375.1	92.2	14.6	98.6	7.8
AD-393247.1	94.4	14.8	103.4	4.0
AD-393257.1	96.2	9.4	101.5	6.0
AD-396459.1	96.4	9.3	104.6	6.7
AD-396450.1	97.5	13.8	99.5	4.6
AD-396445.1	98.6	10.3	97.9	8.8
AD-396461.1	102.7	15.3	105.9	2.4
AD-396452.1	104.4	8.2	99.4	5.6
AD-396913.1	105.9	10.8	91.7	4.1
AD-396455.1	106.3	4.4	100.2	5.5
AD-396912.1	108.0	13.8	95.6	6.8
AD-396915.1	110.6	11.4	98.6	0.8
AD-396453.1	113.6	20.1	101.5	6.3
AD-394991.1	115.6	6.5	101.7	9.5

Table 15. MAPT Single Dose Screens in NEuro2a (mouse) Cells-Screen 4

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-393758.1	13.0	1.9	83.3	33.8
AD-393888.1	18.2	1.8	85.7	14.5
AD-393759.1	14.0	3.5	71.5	13.1
AD-393761.1	20.3	1.9	74.0	13.5
AD-393495.1	17.6	3.2	77.0	11.7
AD-393760.1	21.3	4.1	89.0	10.8
AD-396425.1	9.4	0.9	34.3	8.1
AD-395441.1	13.7	3.8	34.1	4.4
AD-396420.1	16.5	2.5	38.7	7.6
AD-397103.1	25.0	3.6	50.5	15.8
AD-397104.1	17.7	4.3	49.6	9.1
AD-393239.1	40.3	10.7	96.4	15.0
AD-397102.1	20.3	3.4	56.6	7.7
AD-397167.1	26.8	2.8	49.6	11.2
AD-394791.1	48.0	6.0	103.5	21.6
AD-393754.1	32.9	4.5	86.0	23.0
AD-393496.1	13.9	3.7	59.5	10.5
AD-393667.1	14.7	2.5	85.0	18.5
AD-396467.1	17.5	3.9	54.5	12.9

	10 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-393690.1	58.6	15.7	114.5	31.9
AD-396449.1	16.9	2.0	51.3	16.8
AD-393663.1	21.9	6.2	88.8	20.0
AD-393820.1	31.6	3.0	96.0	23.0
AD-396437.1	34.0	4.2	93.0	9.3
AD-393084.1	10.6	1.5	49.0	16.7
AD-396401.1	29.2	1.7	78.9	16.3
AD-394296.1	19.2	3.1	78.3	17.2
AD-395574.1	22.0	2.4	65.4	21.1
AD-393124.1	13.7	3.4	45.9	8.3
AD-393674.1	38.1	13.3	109.3	28.4
AD-396451.1	33.1	4.5	72.5	5.9
AD-396454.1	25.9	4.4	52.2	18.0
AD-393376.1	24.6	6.6	95.6	21.9
AD-393505.1	23.8	1.5	86.4	16.8
AD-393375.1	13.8	0.6	74.5	14.4
AD-393247.1	40.5	3.8	93.2	18.7
AD-393257.1	65.3	5.3	93.0	18.7
AD-396459.1	17.9	1.4	50.9	5.6
AD-396450.1	18.4	1.1	44.0	8.4
AD-396445.1	28.4	3.7	71.9	22.4
AD-396461.1	18.8	2.1	56.7	16.7
AD-396452.1	14.8	1.0	50.1	13.0
AD-396913.1	28.4	3.6	92.6	14.1
AD-396455.1	33.3	6.4	91.5	29.3
AD-396912.1	37.9	2.4	96.0	10.0
AD-396915.1	31.6	4.8	108.7	28.2
AD-396453.1	17.5	1.5	49.1	9.6
AD-394991.1	45.0	5.7	113.4	17.1

Table 16. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 5

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397070.1	ACGUGACCCAAGCU CGCAUGA	1538	512-532	UCAUGCGAGCUTGG GUCACGUGA	1627	510-532
AD-1397071.1	CGUGACCCAAGCUC GCAUGGA	1539	513-533	UCCATGCGAGCUUG GGUCACGUG	1628	511-533
AD-1397072.1	GUGACCCAAGCUCG CAUGGUA	1540	514-534	UACCAUGCGAGCU UGGGUCACGU	1629	512-534
AD-1397073.1	UGACCCAAGCUCGC AUGGUCA	1541	515-535	UGACCATGCGAGCU UGGGUCACG	1630	513-535
AD-1397074.1	GACCCAAGCUCGCA UGGUCAA	1542	516-536	UUGACCAUGCGAG CUUGGGUCAC	1631	514-536

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397075.1	ACCCAAGCUCGCAU GGUCAGA	1543	517-537	UCUGACCAUGCGA GCUUGGGUCA	1632	515-537
AD-1397076.1	CCCAAGCUCGCAUG GUCAGUA	1544	518-538	UACUGACCAUGCG AGCUUGGGUC	1633	516-538
AD-1397077.1	CCAAGCUCGCAUGG UCAGUAA	1545	519-539	UUAAGTACCAUGCG AGCUUGGGU	1634	517-539
AD-1397078.1	CAAGCUCGCAUGGU CAGUAAA	1546	520-540	UUUACUGACCAUG CGAGCUUGGG	1635	518-540
AD-1397079.1	AGUGUGCAAAUAGU CUACAAA	1547	1063-1083	UUUGTAGACUAAU UGCACACUGC	1636	1061-1083
AD-1397080.1	UGCAAAUAGUCUAC AAACCAA	1548	1067-1087	UUGGTUTGUAGACU AUUUGCACA	1637	1065-1087
AD-1397081.1	AUAGUCUACAAACC AGUUGAA	1549	1072-1092	UUCAACTGGUUUG UAGACUAAU	1638	1070-1092
AD-1397082.1	AGUCUACAAACCAG UUGACCA	1550	1074-1094	UGGUCAACUGGUU UGUAGACUAAU	1639	1072-1094
AD-1397083.1	GUCUACAAACCAGU UGACCUA	1551	1075-1095	UAGGTCAACUGGU UUGUAGACUA	1640	1073-1095
AD-1397084.1	AGGCAACAUCCAUC AUAAACA	1552	1125-1145	UGUUTATGAUGGA UGUUGCCUAA	1641	1123-1145
AD-1397085.1	GGCAACAUCCAUCA UAAACCA	1553	1126-1146	UGGUTUAUGAUGG AUGUUGCCUA	1642	1124-1146
AD-1397086.1	GCAACAUCCAUCAU AAACCAA	1554	1127-1147	UUGGTUTAUGAUG GAUGUUGCCU	1643	1125-1147
AD-1397087.1	AACAUCCAUCAUAA ACCAGGA	1555	1129-1149	UCCUGGTUUAUGA UGGAUGUUGC	1644	1127-1149
AD-1397088.1	AUCUGAGAAGCUUG ACUUCAA	1556	1170-1190	UUGAAGTCAAGCU UCUCAGAUUU	1645	1168-1190
AD-1397089.1	CAGCAUCGACAUGG UAGACUA	1557	1395-1415	UAGUCUACCAUGU CGAUGCUGCC	1646	1393-1415
AD-1397090.1	UGGAGCAACAAAG GAUUUGA	1558	1905-1925	UCAAUCCUUUGU UGCUGCCACU	1647	1903-1925
AD-1397091.1	GGCAGCAACAAAGG AUUUGAA	1559	1906-1926	UTCAAATCCUUTGU UGCUGCCAC	1648	1904-1926
AD-1397092.1	AGCAACAAAGGAUU UGAAACA	1560	1909-1929	UGUUTCAAUCCUU UGUUGCUGC	1649	1907-1929
AD-1397093.1	CAACAAAGGAUUUG AAACUUA	1561	1911-1931	UAAGTUTCAAUCC UUUGUUGCU	1650	1909-1931
AD-1397094.1	AACAAAGGAUUUGA AACUUGA	1562	1912-1932	UCAAGUTCAAUCC CUUUGUUGC	1651	1910-1932
AD-1397095.1	ACAAAGGAUUUGAA ACUUGGA	1563	1913-1933	UCCAAGTUCAAU CCUUUGUUG	1652	1911-1933
AD-1397096.1	CAAAGGAUUUGAAA CUUGGUA	1564	1914-1934	UACCAAGUUUCA AUCCUUUGU	1653	1912-1934
AD-1397097.1	AAAGGAUUUGAAAC UUGGUGA	1565	1915-1935	UCACCAAGUUUCA AAUCCUUUGU	1654	1913-1935
AD-1397098.1	AAGGAUUUGAAACU UGGUGUA	1566	1916-1936	UACACCAAGUUTCA AAUCCUUUG	1655	1914-1936
AD-1397099.1	GAUUUGAAACUUGG UGUGUUA	1567	1919-1939	UAACACACCAAGU UUCAAAUCCU	1656	1917-1939
AD-1397101.1	GGCAGACGAUGUCA ACCUUGA	1568	1951-1971	UCAAGGTUGACAUC GUCUGCCUG	1657	1949-1971
AD-1397102.1	AGACGAUGUCAACC UUGUGUA	1569	1954-1974	UACACAAGGUUGA CAUCGUCUGC	1658	1952-1974
AD-1397103.1	GAUGUCAACCUUGU GUGAGUA	1570	1958-1978	UACUCACACAAGG UUGACAUCGU	1659	1956-1978

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397104.1	GCUCCACAGAAACC CUGUUUA	1571	2387-2407	UAAACAGGGUUUC UGUGGAGCAG	1660	2385-2407
AD-1397105.1	UUGAGUUCUGAAGG UUGGAAA	1572	2409-2429	UUUCCAACCUUCAG AACUCAUA	1661	2407-2429
AD-1397106.1	UGAGUUCUGAAGGU UGGAACA	1573	2410-2430	UGUCCAACCUUCA GAACUCAU	1662	2408-2430
AD-1397107.1	UAGGGCUAACAGU UCUCUUA	1574	2469-2489	UAAGAGAACUGGU UAGCCCUAAA	1663	2467-2489
AD-1397108.1	GGGCUAACAGUUC UCUUUGA	1575	2471-2491	UCAAAGAGAACTG GUUAGCCCUA	1664	2469-2491
AD-1397109.1	GGCUAACAGUUCU CUUUGUA	1576	2472-2492	UACAAAGAGAACU GGUUAGCCCU	1665	2470-2492
AD-1397110.1	AACCAGUUCUCUUU GUAAGGA	1577	2476-2496	UCCUTACAAAGAGA ACUGGUUAG	1666	2474-2496
AD-1397111.1	ACCAGUUCUCUUUG UAAGGAA	1578	2477-2497	UUCCTUACAAAGAG AACUGGUUA	1667	2475-2497
AD-1397112.1	CCAGUUCUCUUUGU AAGGACA	1579	2478-2498	UGUCCUTACAAAGA GAACUGGUU	1668	2476-2498
AD-1397113.1	AGUUCUCUUUGUAA GGACUUA	1580	2480-2500	UAAGTCCUUACAAA GAGAACUGG	1669	2478-2500
AD-1397114.1	GUUCUCUUUGUAAG GACUUGA	1581	2481-2501	UCAAGUCCUUACA AAGAGAACUG	1670	2479-2501
AD-1397115.1	UUCUCUUUGUAAGG ACUUGUA	1582	2482-2502	UACAAGTCCUUACA AAGAGAACU	1671	2480-2502
AD-1397116.1	CUCUUUGUAAGGAC UUGUGCA	1583	2484-2504	UGCACAAGUCCTUA CAAAGAGAA	1672	2482-2504
AD-1397117.1	CCAUACUGAGGGUG AAAUUAA	1584	2762-2782	UUAATUTCACCCUC AGUAUGGAG	1673	2760-2782
AD-1397118.1	AUACUGAGGGUGAA AUUAAGA	1585	2764-2784	UCUUAATUUCACCC UCAGUAUGG	1674	2762-2784
AD-1397119.1	ACUGAGGGUGAAAU UAAGGGA	1586	2766-2786	UCCCTUAAUUUCAC CCUCAGUAU	1675	2764-2786
AD-1397120.1	CUGAGGGUGAAAUU AAGGGAA	1587	2767-2787	UTCCCTAAUUTCA CCCUCAGUA	1676	2765-2787
AD-1397121.1	UGAGGGUGAAAUUA UGGGAAA	1588	2768-2788	UUUCCCTUAAUUUC ACCCUCAGU	1677	2766-2788
AD-1397122.1	GAGGGUGAAAUUAA GGGAAGA	1589	2769-2789	UCUCCCCUAAUUU UCACCCUCAG	1678	2767-2789
AD-1397123.1	GCCUCUCACUCUCA GUUCCAA	1590	2819-2839	UUGGAACUGAGAG UGAGAGGCUG	1679	2817-2839
AD-1397124.1	CUCUCACUCUCAGU UCCACUA	1591	2821-2841	UAGUGGAACUGAG AGUGAGAGGC	1680	2819-2841
AD-1397125.1	UCUCAGUCCACUC AUCCAAA	1592	2828-2848	UUUGGATGAGUGG AACUGAGAGU	1681	2826-2848
AD-1397126.1	UAGGUGUUUCUGCC UUGUUGA	1593	2943-2963	UCAACAAGGCAGA AACACCUAGG	1682	2941-2963
AD-1397127.1	AGGUGUUUCUGCCU UGUUGAA	1594	2944-2964	UTCAACAAGGCAGA AACACCUAG	1683	2942-2964
AD-1397128.1	GUGUUUCUGCCUUG UUGACAA	1595	2946-2966	UUGUCAACAAGGC AGAAACACCU	1684	2944-2966
AD-1397129.1	UGUUUCUGCCUUGU UGACAUU	1596	2947-2967	UAUGTCAACAAGGC AGAAACACC	1685	2945-2967
AD-1397130.1	GAAGCCAUGCUGUC UGUUCUA	1597	3252-3272	UAGAACAGACAGC AUGGCUUCCA	1686	3250-3272
AD-1397131.1	AGCAGCUGAACAUU UACAUAA	1598	3277-3297	UUAUGUAUAUGUU CAGCUGCUC	1687	3275-3297

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397132.1	AGCUGAACAUUAUACAUAGAU	1599	3280-3300	UAUCTATGUAUAUGUUCAGCUGC	1688	3278-3300
AD-1397133.1	GCUGAACAUUAUACA UAGAUGA	1600	3281-3301	UCAUCUAUGUATAUGUUCAGCUG	1689	3279-3301
AD-1397134.1	CUGAACAUUAUACAUAGAUGUA	1601	3282-3302	UACATCTAUGUAUAUGUUCAGCU	1690	3280-3302
AD-1397135.1	GAACAUUAUACAUAUGUUGA	1602	3284-3304	UCAACATCUAUGUAUAUGUUCAG	1691	3282-3304
AD-1397136.1	AACAUUAUACAUAUGAUGUUGCA	1603	3285-3305	UGCAACAUCUAUGUAUAUGUUC	1692	3283-3305
AD-1397137.1	ACAUAUAUACAUAUGAUGUUGCA	1604	3286-3306	UGGCAACAUCUAUGUAUAUGUUC	1693	3284-3306
AD-1397138.1	GAGUUGUAGUUGGAUUUGUCA	1605	3331-3351	UGACAAAUCCAACUACAACUCA	1694	3329-3351
AD-1397139.1	AGUUGUAGUUGGAUUGUCUA	1606	3332-3352	UAGACAAAUCCAACUACAACUCA	1695	3330-3352
AD-1397140.1	GUUGUAGUUGGAUUGUCUGA	1607	3333-3353	UCAGACAAAUCCAACUACAACUC	1696	3331-3353
AD-1397141.1	UUGUAGUUGGAUUUGUCUGUA	1608	3334-3354	UACAGACAAAUCCAACUACAACUC	1697	3332-3354
AD-1397142.1	UGUAGUUGGAUUUGUCUGUA	1609	3335-3355	UACAGACAAAUCCAACUACAAC	1698	3333-3355
AD-1397143.1	GUAGUUGGAUUUGUCUGUUA	1610	3336-3356	UAAACAGACAAAUCCAACUACAA	1699	3334-3356
AD-1397144.1	AGUUGGAUUUGUCUGUUA	1611	3338-3358	UAUAAACAGACAAAUCCAACUAC	1700	3336-3358
AD-1397145.1	UUGGAUUUGUCUGUUAUGCA	1612	3340-3360	UGCATAAACAGACAUAUCCAACU	1701	3338-3360
AD-1397146.1	GGAUUUGUCUGUUAUGCUUA	1613	3342-3362	UAAGCATAAACAGACAAAUCCA	1702	3340-3362
AD-1397147.1	GAUUUGUCUGUUAUGCUUGA	1614	3343-3363	UCAAGCAUAAACAGACAAAUCCA	1703	3341-3363
AD-1397148.1	AUUUGUCUGUUAUGCUUGGA	1615	3344-3364	UCCAAGCAUAAACAGACAAAUCCA	1704	3342-3364
AD-1397149.1	UUUGUCUGUUAUGCUUGGAA	1616	3345-3365	UCCAAGCAUAAACAGACAAAUCCA	1705	3343-3365
AD-1397150.1	UUGUCUGUUAUGCUUGGAUA	1617	3346-3366	UAUCCAAGCAUAAACAGACAAAU	1706	3344-3366
AD-1397151.1	UGUCUGUUAUGCUUGGAUUA	1618	3347-3367	UAAUCCAAGCAUAAACAGACAAA	1707	3345-3367
AD-1397152.1	UCUGUUUAUGCUUGGAUUA	1619	3349-3369	UUGAAUCCAAGCAUAAACAGACA	1708	3347-3369
AD-1397153.1	GAUUUUAUGCUUGGAUUA	1620	3350-3370	UGUGAATCCAAGCAUAAACAGAC	1709	3348-3370
AD-1397154.1	UUUAUGCUUGGAUUAUACACCA	1621	3353-3373	UCUGGUGAAUCCAAGCAUAAACA	1710	3351-3373
AD-1397155.1	AUUCACCAGAGUGACUAUGAA	1622	3364-3384	UUCATAGUCACUCUGGUGAAUCC	1711	3362-3384
AD-1397156.1	UCACCAGAGUGACUAUGAUA	1623	3366-3386	UUAUCATAGUCACUCUGGUGAAU	1712	3364-3386
AD-1397157.1	CACCAGAGUGACUAUGAUAGA	1624	3367-3387	UCUATCAUAGUCACUCUGGUGAA	1713	3365-3387
AD-1397158.1	ACCAGAGUGACUAUGAUAGUA	1625	3368-3388	UACUAUCAUAGUCACUCUGGUGA	1714	3366-3388
AD-1397159.1	CCAGAGUGACUAUGAUAGUGA	1626	3369-3389	UACTATCAUAGUCACUCUGGUG	1715	3367-3389

Table 17. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 5

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397070.1	ascsgug(Ahd)ccCfAfAfgcucgcaugaL96	1716	VPusdCsaudGcdGagcudTgGfgucacgusgsa	1805	UCACGUGACCCAA GCUCGCAUGG	1894
AD-1397071.1	csgsuga(Chd)ccAfAfGfcucgcauggaL96	1717	VPusCfscadTg(C2p)gagc uuGfgGfucacgsusg	1806	CACGUGACCCAAG CUCGCAUGGU	1895
AD-1397072.1	gsusgac(Chd)caAfGfCfucgcaugguaL96	1718	VPusAfsccdAu(G2p)cga gcuUfgGfgucacsusu	1807	ACGUGACCCAAGC UCGCAUGGUC	1896
AD-1397073.1	usgsacc(Chd)aaGfCfUfcgcauggucaL96	1719	VPusdGsacdCadTgcgad GcUfugggucacsosg	1808	CGUGACCCAAGCU CGCAUGGUCA	1897
AD-1397074.1	gsasccc(Ahd)agCfUfCfcgcauggucaL96	1720	VPusUfsgadCe(Agn)ugc gagCfuUfggucacsasc	1809	GUGACCCAAGCUC GCAUGGUCAG	1898
AD-1397075.1	ascseca(Ahd)gcUfCfGfcgcauggucaL96	1721	VPusdCsugdAcCdCaugcd GaGfcuuggguscsa	1810	UGACCCAAGCUCG CAUGGUCAGU	1899
AD-1397076.1	cscscaa(Ghd)cuCfGfCfcgcauggucaL96	1722	VPusAfsudGa(C2p)cau gcgAfgCfuugggsusc	1811	GACCCAAGCUCGC AUGGUCAGUA	1900
AD-1397077.1	cscsaag(Chd)ucGfCfAfcgcauggucaL96	1723	VPusUfsacdTg(Agn)cca ugcGfaGfcuuggsgsu	1812	ACCCAAGCUCGCA UGGUCAGUAA	1901
AD-1397078.1	csasagc(Uhd)cgCfAfUfcgcauggucaL96	1724	VPusUfsuadCu(G2p)acc augCfGfGfcuuggsgsg	1813	CCCAAGCUCGCAU GGUCAGUAAA	1902
AD-1397079.1	asgsugu(Ghd)caAfAfUfcgcauggucaL96	1725	VPusUfsugdTa(G2p)acu auuUfgCfGfcuuggsgsc	1814	GCAGUGUGCAAAU AGUCUACAAA	1903
AD-1397080.1	usgscaa(Ahd)uaGfUfcfuacaaccaaL96	1726	VPusUfsggdTu(Tgn)gua gacUfaUfugcacsca	1815	UGUGCAAAUAGUC UACAAACCAG	1904
AD-1397081.1	asusagu(Chd)uaCfAfAfcgcauggucaL96	1727	VPusUfscadAc(Tgn)ggg uugUfaGfGfcuuggsgsu	1816	AAAUAGUCUACAA ACCAGUUGAC	1905
AD-1397082.1	asgsucu(Ahd)caAfAfCfcgcauggucaL96	1728	VPusGfsgudCa(Agn)cug guuUfgUfagacusas	1817	AUAGUCUACAAAC CAGUUGACCU	1906
AD-1397083.1	gsuscua(Chd)aaAfCfCfcgcauggucaL96	1729	VPusAfsugdTe(Agn)acu gguUfuGfugacgsusa	1818	UAGUCUACAAACC AGUUGACCUG	1907
AD-1397084.1	asgsuca(Chd)caUfCfCfcgcauggucaL96	1730	VPusGfsuudTa(Tgn)gau ggaUfgUfugccusasa	1819	UUAGGCAACAUCU AUCAUAAACC	1908
AD-1397085.1	gsgscaa(Chd)auCfCfAfcgcauggucaL96	1731	VPusGfsgudTu(Agn)uga uggAfuGfugccsusa	1820	UAGGCAACAUCU UCAUAAACCA	1909
AD-1397086.1	gsesaac(Ahd)ucCfAfUfcgcauggucaL96	1732	VPusUfsggdTu(Tgn)aug augGfaUfguugcsusu	1821	AGGCAACAUCUCC AUUAAACCAG	1910
AD-1397087.1	asascu(Chd)caUfCfAfcgcauggucaL96	1733	VPusCfscudGg(Tgn)uuu ugaUfgGfugcgsusc	1822	GCAACAUCUCCA UAAACCAGGA	1911
AD-1397088.1	asuscug(Ahd)gaAfGfCfcgcauggucaL96	1734	VPusUfsgadAg(Tgn)caa gcuUfcUfcagaususu	1823	AAAUCUGAGAAGC UUGACUUCUA	1912
AD-1397089.1	csasgca(Uhd)cgAfCfAfcgcauggucaL96	1735	VPusAfsudCu(Agn)cca uguCfGfugcgsusc	1824	GGCAGCAUCGACA UGGUAGACUC	1913
AD-1397090.1	usgsuca(Chd)caAfCfAfcgcauggucaL96	1736	VPusdCsaadAudCcuuud GuUfgcugccsusu	1825	AGUGGCAGCAACA AAGGAUUUGA	1914
AD-1397091.1	gsgscag(Chd)aaAfAfAfcgcauggucaL96	1737	VPusdTsacdAadTccuud TgUfugcugccsusc	1826	GUGGCAGCAACAA AGGAUUUGAA	1915
AD-1397092.1	asgscaa(Chd)aaAfGfGfcgcauggucaL96	1738	VPusGfsuudTe(Agn)aa uccuUfuGfugcgsusc	1827	GCAGCAACAAAGG AUUUGAAACU	1916
AD-1397093.1	csasaca(Ahd)agGfAfUfcgcauggucaL96	1739	VPusAfsagdTu(Tgn)caaa ucCfuUfugcgsusu	1828	AGCAACAAAGGAU UUGAAACUUG	1917
AD-1397094.1	asascaa(Ahd)ggAfUfUfcgcauggucaL96	1740	VPusdCsaadGudTucaad AaCfcuugcgsusc	1829	GCAACAAAGGAUU UGAAACUUGG	1918
AD-1397095.1	ascsaac(Chd)gaUfUfUfcgcauggucaL96	1741	VPusdCsacdAgdTuucad AaUfcuugcgsusc	1830	CAACAAAGGAUUU GAAACUUGGU	1919

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397096.1	csasaag(Ghd)auUfUfGfaaacuugguaL96	1742	VPusdAscedAadGnuucdAaAfuccuuugsusu	1831	AACAAAGGAUUUGAAACUUGGUG	1920
AD-1397097.1	asasagg(Ahd)uuUfGfAfaacuugguaL96	1743	VPusdCsacdCadAguuudCaAfauccuuugsu	1832	ACAAAGGAUUUGAAACUUGGUGU	1921
AD-1397098.1	asasgga(Uhd)uuGfAfAfacuugguaL96	1744	VPusdAscadCedAaguudTcAfauccuuusug	1833	CAAAGGAUUUGAAACUUGGUGUG	1922
AD-1397099.1	gsasuuu(Ghd)aaAfCfUfugguguguaL96	1745	VPusAfsacdAc(Agn)ccaaguUfuCfaauescsu	1834	AGGAUUUGAAACUUGGUGUGUUC	1923
AD-1397101.1	gsgscag(Ahd)cgAfUfGfucaaccuugaL96	1746	VPusCfsaadGg(Tgn)ugaauCfGfucgccsusg	1835	CAGGCAGACGAUGUCAACCUUGU	1924
AD-1397102.1	asgsacg(Ahd)ugUfCfAfacuuguguaL96	1747	VPusdAscadCadAgguudGaCfaucgucugsc	1836	GCAGACGAUGUCAACCUUGUGUG	1925
AD-1397103.1	gsasugu(Chd)aaCfCfUfuguguguaL96	1748	VPusAfsacdCa(C2p)acaaUfGfacaucsgsu	1837	ACGAUGUCAACCUUGUGUGAGUG	1926
AD-1397104.1	gsesucc(Ahd)caGfAfAfacuccuuaL96	1749	VPusAfsaadCa(G2p)gguuuUfGfaggagesasg	1838	CUGCUCACAGAAACCCUGUUUU	1927
AD-1397105.1	ususgag(Uhd)ucUfGfAfagguuggaaaL96	1750	VPusUfsucdCa(Agn)ccuuaGfAfcauasasa	1839	UAUUGAGUUCUGAAGGUUGGAAC	1928
AD-1397106.1	usgsagu(Uhd)cuGfAfAfgguuggaacaL96	1751	VPusGfsuudCc(Agn)accuuUfGfAcucasasu	1840	AUUGAGUUCUGAAGGUUGGAACU	1929
AD-1397107.1	usasggg(Chd)uaAfCfCfaguucucuuaL96	1752	VPusdAsagdAgdAacugdGuUfageccuasasa	1841	UUUAGGGCUAACCAGUUCUCUUU	1930
AD-1397108.1	gsgsgcu(Ahd)acCfAfGfuucucuugaL96	1753	VPusdCsaadAgdAgaacdTgGfuuaagccsusa	1842	UAGGGCUAACCAGUUCUCUUUGU	1931
AD-1397109.1	gsgscua(Ahd)ccAfGfUfucucuugaL96	1754	VPusdAscadAadGagaadCuGfuuagccscsu	1843	AGGGCUAACCAGUUCUCUUUGUA	1932
AD-1397110.1	asascca(Ghd)uuCfUfCfuuuuaaggaL96	1755	VPusdCscudTadCaaagdAgAfacugguasag	1844	CUAACCAGUUCUCUUUUAAGGA	1933
AD-1397111.1	ascsag(Uhd)ucUfCfUfuuuaaggaL96	1756	VPusUfscdTu(Agn)caaaGfAfcugguasasa	1845	UAACCAGUUCUCUUUGUAAGGAC	1934
AD-1397112.1	csesagu(Uhd)cuCfUfUfuguaggaL96	1757	VPusGfsucdCu(Tgn)acaaagAfgAfacuggsusu	1846	AACCAGUUCUCUUUGUAAGGACU	1935
AD-1397113.1	asgsuuc(Uhd)cuUfUfGfuuaaggacuuaL96	1758	VPusAfsagdTc(C2p)uuacaaAfgAfgaacusgsg	1847	CCAGUUCUCUUUGUAAGGACUUG	1936
AD-1397114.1	gsusucu(Chd)uuUfGfUfaaggacuugaL96	1759	VPusCfsaadGu(C2p)cuuacaAfaGfagaacsug	1848	CAGUUCUCUUUGUAAGGACUUGU	1937
AD-1397115.1	ususcuc(Uhd)uuGfUfAfaggacuugaL96	1760	VPusAfsacdAg(Tgn)ccuuacAfaAfgagaacsu	1849	AGUUCUCUUUGUAAGGACUUGUG	1938
AD-1397116.1	csuscuu(Uhd)guAfAfGfgacuugucaL96	1761	VPusdGscadCadAguccdTuAfaaaagagsasa	1850	UUCUCUUUGUAAGGACUUGGCC	1939
AD-1397117.1	csesaua(Chd)ugAfGfGfgugaaaauaaL96	1762	VPusUfsaadTu(Tgn)caccuCFaGfuauggsasg	1851	CUCCAUAACUGAGGUGUAAAUA	1940
AD-1397118.1	asusacu(Ghd)agGfGfUfgaaaauaagaL96	1763	VPusdCsuudAadTuucadCcCfucagauusgsg	1852	CCAUACUGAGGGUGAAAUAAGG	1941
AD-1397119.1	ascsuga(Ghd)ggUfGfAfaauuaaggaL96	1764	VPusdCscdTuAauuudCaCfccucagusasu	1853	AUACUGAGGGUGAAGAAUAAGGGA	1942
AD-1397120.1	csusgag(Ghd)guGfAfAfaauaaggaL96	1765	VPusdTscdCuTaauudTcAfccucagsusa	1854	UACUGAGGGUGAAGAAUAAGGGAA	1943
AD-1397121.1	usgsagg(Ghd)ugAfAfAfuuaagggaaaL96	1766	VPusUfsucdCc(Tgn)uauuuCfCfccucagsu	1855	ACUGAGGGUGAAGAAUAAGGGAAG	1944
AD-1397122.1	gsasggg(Uhd)gaAfAfUfuaaggaagaL96	1767	VPusCfsuudCc(C2p)uuauuUfCfaccucagsg	1856	CUGAGGGUGAAGAAUAAGGGAAGG	1945
AD-1397123.1	gsescuc(Uhd)caCfUfCfucaguuecaL96	1768	VPusUfsggdAa(C2p)ugagUfgAfgagcsusg	1857	CAGCCUCUCACUCUCAGUCCAC	1946
AD-1397124.1	csuscuc(Ahd)cuCfUfCfaguuccacuaL96	1769	VPusAfsudGg(Agn)acugagAfgUfgagagsgsc	1858	GCCUCUCACUCUCAGUCCACUC	1947

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397125.1	usesuca(Ghd)uuCfCfAfcucauccaaaL96	1770	VPusUfsugdGa(Tgn)gaguggAfaCfugagasgsu	1859	ACUCUCAGUCCA CUCAUCCAAC	1948
AD-1397126.1	usasgu(Ghd)uuUfCfUfgccuuguugaL96	1771	VPusdCsaadCadAggcadGaAfaacaccuasgsg	1860	CCUAGUGUUUCU GCCUUGUUGA	1949
AD-1397127.1	asgsug(Uhd)uuCfUfGfccuuguugaL96	1772	VPusdTscadAcdAaggcdAgAfaacaccuasg	1861	CUAGGUGUUUCUG CCUUGUUGAC	1950
AD-1397128.1	gsusguu(Uhd)cuGfCfCfuuguugacaaL96	1773	VPusUfsgudCa(Agn)caaggcAfgAfaacacsu	1862	AGGUGUUUCUGCC UUGUUGACAU	1951
AD-1397129.1	usgsuuu(Chd)ugCfCfUfuguugacauaL96	1774	VPusAfsugdTe(Agn)acaaggCfaGfaacacsu	1863	GGUGUUUCUGCCU UGUUGACAUG	1952
AD-1397130.1	gsasagc(Chd)auGfCfUfgucuguucuaL96	1775	VPusAfsgadAc(Agn)gacagcAfuGfgeucscsa	1864	UGGAAGCCAUGCU GUCUGUUCUG	1953
AD-1397131.1	asgscag(Chd)ugAfAfCfauauacauaaL96	1776	VPusUfsaudGu(Agn)uauuuCfaGfcugcuscsc	1865	GGAGCAGCUGAAC AUUAACAUG	1954
AD-1397132.1	asgscug(Ahd)acAfUfAfuacauagauaL96	1777	VPusdAsucdTadTguaudAuGfuucagcugsc	1866	GCAGCUGAACAU UACAUGAUG	1955
AD-1397133.1	gscsuga(Ahd)caUfAfUfacaugaugaL96	1778	VPusdCsaadCudAuguadTaUfguucagcsusg	1867	CAGCUGAACAU ACAUGAUGU	1956
AD-1397134.1	csusgaa(Chd)auAfUfAfcuagauaL96	1779	VPusAfsadTc(Tgn)auguauAfUfGfuucagcsu	1868	AGCUGAACAU CAUAGAUGU	1957
AD-1397135.1	gsasaca(Uhd)auAfCfAfuagauugaL96	1780	VPusdCsaadCadTcuauGuAfuaugucsasg	1869	CUGAACAU UAGAUGUUGC	1958
AD-1397136.1	asascu(Ahd)uaCfAfUfagaugugcaL96	1781	VPusGfscadAc(Agn)ucuaugUfaUfauuguscsa	1870	UGAACAU AGAUGUUGCC	1959
AD-1397137.1	ascsaau(Uhd)acAfUfAfgaugugccaL96	1782	VPusGfsgcdAa(C2p)aucuauGfuAfuaugusuc	1871	GAACAU GAUGUUGCCC	1960
AD-1397138.1	gsasguu(Ghd)uaGfUfUfggaauugucaL96	1783	VPusdGsacdAadAuccadAcUfaacucscsa	1872	UUGAGUUGUAGU GGAUUUGUCU	1961
AD-1397139.1	asgsuug(Uhd)agUfUfGfgauuugucuaL96	1784	VPusdAsgadCadAauccdAaCfuacaucscsa	1873	UGAGUUGUAGU GAUUUGUCUG	1962
AD-1397140.1	gsusugu(Ahd)guUfGfGfauuugucugaL96	1785	VPusdCsagdAcdAauacdCaAfcuacaucscu	1874	GAGUUGUAGU AUUUGUCUGU	1963
AD-1397141.1	ususgua(Ghd)uuGfGfAfuugucuguaL96	1786	VPusAfsadGa(C2p)aaauccAfaCfuacaucscu	1875	AGUUGUAGU UUUGUCUGU	1964
AD-1397142.1	usgsuag(Uhd)ugGfAfUfuugucuguuaL96	1787	VPusAfsadAg(Agn)caauccCfaAfcuacasc	1876	GUUGUAGU UUGUCUGUUU	1965
AD-1397143.1	gsusagu(Uhd)ggAfUfUfugucuguuuuL96	1788	VPusAfsaadCa(G2p)acaaucCfCfAfaucscsa	1877	UUGUAGU UGUCUGUUUA	1966
AD-1397144.1	asgsuug(Ghd)auUfUfGfucuguuuuaL96	1789	VPusdAsuadAadCagacdAaAfucaacusc	1878	GUAGUUGGAU UCUGUUUAUG	1967
AD-1397145.1	ususgga(Uhd)uuGfUfCfuguuuuugcaL96	1790	VPusdGscadTadAacagdAcAfaucacscu	1879	AGUUGGAU UGUUUAUGCU	1968
AD-1397146.1	gsasuuu(Uhd)guCfUfGfuuuuugcuuaL96	1791	VPusAfsagdCa(Tgn)aaacagAfcAfaucscsa	1880	UUGGAU UUUAUGCUUG	1969
AD-1397147.1	gsasuuu(Ghd)ucUfGfUfuuuuugcuugaL96	1792	VPusCfsaadGc(Agn)uaaacaGfaCfaucscsa	1881	UGGAU UUAUGCUUGG	1970
AD-1397148.1	asusuug(Uhd)cuGfUfUfuaugcuuggaL96	1793	VPusCfscadAg(C2p)auaaacAfgAfaaauscsc	1882	GGAU UAUGCUUGGA	1971
AD-1397149.1	ususugu(Chd)ugUfUfUfauugcuuggaL96	1794	VPusUfscadAa(G2p)cauaaaCfaGfaaauscsc	1883	GAU AUGCUUGGAU	1972
AD-1397150.1	usuguc(Uhd)guUfUfAfuugcuuggaL96	1795	VPusdAsucdCadAgcaudAaAfcagacaasasu	1884	AUUUGUCUGUU UGCUUGGAU	1973
AD-1397151.1	usgsucu(Ghd)uuUfAfUfgeuuggaL96	1796	VPusAfsaudCc(Agn)agcauaAfaCfagacasa	1885	UUUGUCUGUU GCUUGGAUUC	1974
AD-1397152.1	usesugu(Uhd)uaUfGfCfuuggaucuaL96	1797	VPusUfsgadAu(C2p)caagcaUfaAfacagascsa	1886	UGUCUGUUUA UUGGAUUCAC	1975

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397153.1	csusguu(Uhd)auGfCfUfuggauucacaL96	1798	VPusGfsugdAa(Tgn)ccaagcAfuAfaacagsasc	1887	GUCUGUUUAUGCUUGGAUUCACC	1976
AD-1397154.1	ususuuu(Ghd)cuUfGfGfauucaccagaL96	1799	VPusCfsugdGu(G2p)aaucacAfgCfauaaascsa	1888	UGUUUAUGCUUGGAUUCACCAGA	1977
AD-1397155.1	asusuca(Chd)caGfAfGfugacuugaaL96	1800	VPusUfscadTa(G2p)ucacucUfgGfugaauuscsc	1889	GGAUUCACCAGAGUGACUAUGAU	1978
AD-1397156.1	uscsacc(Ahd)gaGfUfGfacuugauuaaL96	1801	VPusUfsaudCa(Tgn)agucacUfcUfggugasasu	1890	AUUCACCAGAGUGACUAUGAUAG	1979
AD-1397157.1	csascca(Ghd)agUfGfAfacuugauagaL96	1802	VPusCfsuadTc(Agn)uagucaCfuCfuggugsasa	1891	UUCACCAGAGUGACUAUGAUAGU	1980
AD-1397158.1	ascscag(Ahd)guGfAfCfuaugauaguaL96	1803	VPusAfsudAu(C2p)auagucAfcUfcuggusgsa	1892	UCACCAGAGUGACUAUGAUAGUG	1981
AD-1397159.1	cscsaga(Ghd)ugAfCfUfaugauagugaL96	1804	VPusdCsacdTadTcauadGuCfacucuggsusg	1893	CACCAGAGUGACUAUGAUAGUGA	1982

Table 18. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 6

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397160.1	CAGAGUGACUAUGAUAGUGAA	1983	3370-3390	UTCACUAUCAUAGUCA CUCUGGU	2073	3368-3390
AD-1397161.1	GGACGCAUGUAUCUUGAAAUA	1984	3412-3432	UAUUTCAAGAUACAUG CGUCCUU	2074	3410-3432
AD-1397162.1	ACGCAUGUAUCUU GAAAUGCA	1985	3414-3434	UGCATUTCAAGAUACA UGCGUCC	2075	3412-3434
AD-1397163.1	CGCAUGUAUCUUG AAAUGCUA	1986	3415-3435	UAGCAUTUCAAGAUAC AUGCGUC	2076	3413-3435
AD-1397164.1	GCAUGUAUCUUGA AAUGCUUA	1987	3416-3436	UAAGCATUUCAAGUA CAUGCGU	2077	3414-3436
AD-1397165.1	CAUGUAUCUUGAA AUGCUUGA	1988	3417-3437	UCAAGCAUUUCAAGAU ACAUGCG	2078	3415-3437
AD-1397166.1	UGUAUCUUGAAAU GCUUGUAA	1989	3419-3439	UUACAAGCAUUUCAAG AUACAUG	2079	3417-3439
AD-1397167.1	GUAUCUUGAAAUG CUUGUAAA	1990	3420-3440	UUUACAAGCAUUUCAA GAUACAU	2080	3418-3440
AD-1397168.1	CUUGAAAUGCUUG UAAAGAGA	1991	3424-3444	UCUCTUTACAAGCAUU UCAAGAU	2081	3422-3444
AD-1397169.1	UUGAAAUGCUUGU AAAGAGGA	1992	3425-3445	UCCUCUTUACAAGCAU UUCAAGA	2082	3423-3445
AD-1397170.1	UGAAAUGCUUGUA AAGAGGUA	1993	3426-3446	UACCTCTUUACAAGCA UUUCAAG	2083	3424-3446
AD-1397171.1	GAAAUGCUUGUAA AGAGGUUA	1994	3427-3447	UAACCUCUUUACAAGC AUUUCAA	2084	3425-3447
AD-1397172.1	AAAUGCUUGUAAA GAGGUUUA	1995	3428-3448	UAAACCTCUUACAAG CAUUUCA	2085	3426-3448
AD-1397173.1	AAUGCUUGUAAAG AGGUUUCA	1996	3429-3449	UGAAACCUCUUUACAA GCAUUUC	2086	3427-3449
AD-1397174.1	AUGCUUGUAAAGA GGUUUCUA	1997	3430-3450	UAGAAACCUCUTUACA AGCAUUU	2087	3428-3450
AD-1397175.1	UGCUUGUAAAGAG GUUUCUAA	1998	3431-3451	UTAGAAACCUCTUUAC AAGCAUU	2088	3429-3451
AD-1397176.1	UUGUAAAGAGGUU UCUAACCA	1999	3434-3454	UGGUTAGAAACCUCUU UACAAGC	2089	3432-3454

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6
AD-1397177.1	AUUGCUGCCUAAA GAAACUCA	2000	4132-4152	UGAGTUTCUUUAGGCA GCAAUGU	2090	4130-4152
AD-1397178.1	UGCUGCCUAAAGA AACUCAGA	2001	4134-4154	UCUGAGTUUCUUUAGG CAGCAAU	2091	4132-4154
AD-1397179.1	UCUGGUUUGGGUA CAGUUA	2002	4179-4199	UUUAAC TGUACCCAAA CCAGAAG	2092	4177-4199
AD-1397180.1	GGUUUGGUACAG UUAAGGA	2003	4182-4202	UCCUTU AACUGTACCCA AACCAG	2093	4180-4202
AD-1397181.1	UUUGGUACAGUU AAAGGCAA	2004	4184-4204	UUGCCUTU AACUGUAC CCAAACC	2094	4182-4204
AD-1397182.1	GAUUUGGUGGUGG UUAGAGAA	2005	4395-4415	UTCUCU AACACCACCA AAUCUA	2095	4393-4415
AD-1397183.1	UCAUUACUGCCAA CAGUUUCA	2006	4425-4445	UGAAACTGUUGGCAGU AAUGAGG	2096	4423-4445
AD-1397184.1	CAUUACUGCCAAC AGUUUCGA	2007	4426-4446	UCGAAACUGUUGGCAG UUAUGAG	2097	4424-4446
AD-1397185.1	UACUGCCAACAGU UUCGGCUA	2008	4429-4449	UAGCCG AACUGUUGG CAGUAAU	2098	4427-4449
AD-1397186.1	GUUCCUCU UCCUG AAGUUCUA	2009	4469-4489	UAGA ACTUCAGGAAGA GGAACCG	2099	4467-4489
AD-1397187.1	UUCCUCU UCCUGA AGUUCUUA	2010	4470-4490	UAAGA ACUUCAGGAAG AGGAACC	2100	4468-4490
AD-1397188.1	UCCUCU UCCUGAA GUUCUUGA	2011	4471-4491	UCAAGA ACUUCAGGAA GAGGAAC	2101	4469-4491
AD-1397189.1	CCUCU UCCUGAAG UUCUUGUA	2012	4472-4492	UACAAGA ACUUCAGGA AGAGGAA	2102	4470-4492
AD-1397190.1	CUCU UCCUGAAGU UCUUGUGA	2013	4473-4493	UCACAAGA ACUTCAGG AAGAGGA	2103	4471-4493
AD-1397191.1	UCU UCCUGAAGUU CUUGUGCA	2014	4474-4494	UGCACAAGA ACTUCAG GAAGAGG	2104	4472-4494
AD-1397192.1	CCAGCCUAAGAUC AUGGUUUA	2015	4569-4589	UAAACCAUGAUCUUAG GCUGGCC	2105	4567-4589
AD-1397193.1	AGCCUAAGAUCAU GGUUUAGA	2016	4571-4591	UCUAAAACCAUGAUCUU AGGCUGG	2106	4569-4591
AD-1397194.1	GCCUAAGAUAUG GUUUAGGA	2017	4572-4592	UCCUAAAACCAUGAUCU UAGGCUG	2107	4570-4592
AD-1397195.1	UCAGUGCUGGCAG AUAAAUA	2018	4596-4616	UAAUTUAUCUGCCAGC ACUGAUC	2108	4594-4616
AD-1397196.1	CACGCUGGCUUGU GAUCUUA	2019	4623-4643	UUAAGATCACAAGCCA GCGUGCC	2109	4621-4643
AD-1397197.1	UGGGCUAGAUAGG AUAUACUA	2020	4721-4741	UAGUAUAUCCUAUCUA GCCCACC	2110	4719-4741
AD-1397198.1	GGGCUAGAUAGGA UAUACUGA	2021	4722-4742	UCAGTATAUCCTAUCUA GCCCCAC	2111	4720-4742
AD-1397199.1	CUAGAUAGGAUAU ACUGUAUA	2022	4725-4745	UAUACAGUAUAUCCUA UCUAGCC	2112	4723-4745
AD-1397200.1	UAGAUAGGAUAUA CUGUAUGA	2023	4726-4746	UCAUACAGUAUAUCCU AUCUAGC	2113	4724-4746
AD-1397201.1	ACUCACUUUAUCA AUAGUUCA	2024	4766-4786	UGAACUAUUGATAAAG UGAGUCA	2114	4764-4786
AD-1397202.1	CUCACUUUAUCAA UAGUCCA	2025	4767-4787	UGGAACTAUUGAUAAA GUGAGUC	2115	4765-4787
AD-1397203.1	UCACUUUAUCAU AGUCCAA	2026	4768-4788	UUGGAACUAUUGAUAA AGUGAGU	2116	4766-4788
AD-1397204.1	CACUUUAUCAUA GUUCCAUA	2027	4769-4789	UAUGGAACUAUUGAUA AAGUGAG	2117	4767-4789

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6
AD-1397205.1	ACUUUAUCAAUAG UCCAUUA	2028	4770-4790	UAAUGGAACUAUUGAU AAAGUGA	2118	4768-4790
AD-1397206.1	AUAGUCCAUAUUA AAUUGACA	2029	4779-4799	UGUCAATUAAAUGGA ACUAUUG	2119	4777-4799
AD-1397207.1	GGUGAGACUGUAU CCUGUUUA	2030	4805-4825	UAAACAGGAUACAGUC UCACCAC	2120	4803-4825
AD-1397208.1	GUGAGACUGUAUC CUGUUUGA	2031	4806-4826	UCAAACAGGAUACAGU CUCACCA	2121	4804-4826
AD-1397209.1	UGAGACUGUAUCC UGUUUGCA	2032	4807-4827	UGCAAACAGGATACAG UCUCACC	2122	4805-4827
AD-1397210.1	GAGACUGUAUCCU GUUUGCUA	2033	4808-4828	UAGCAAACAGGAUACA GUCUCAC	2123	4806-4828
AD-1397211.1	AGACUGUAUCCUG UUUGCUAA	2034	4809-4829	UTAGCAAACAGGAUAC AGUCUCA	2124	4807-4829
AD-1397212.1	CUGUAUCCUGUUU GCUAUUGA	2035	4812-4832	UCAATAGCAAACAGGA UACAGUC	2125	4810-4832
AD-1397213.1	UGUAUCCUGUUUG CUAUUGCA	2036	4813-4833	UGCAAUAGCAAACAGG AUACAGU	2126	4811-4833
AD-1397214.1	GUAUCCUGUUUGC UAUUGCUA	2037	4814-4834	UAGCAATAGCAAACAG GAUACAG	2127	4812-4834
AD-1397215.1	UGAUUUCACACCAC AUUUGCUA	2038	4936-4956	UAGCAAAUGUGGUUGA AAUCAUG	2128	4934-4956
AD-1397216.1	UAUGGACAUCUGG UUGCUUUA	2039	5072-5092	UAAAGCAACCAGAUGU CCAUAUU	2129	5070-5092
AD-1397217.1	AUGGACAUCUGGU UGCUUUGA	2040	5073-5093	UCAAAGCAACCAGAUG UCCAUAU	2130	5071-5093
AD-1397218.1	ACUUCUGAUUUCU CUUCAGCA	2041	5345-5365	UGCUGAAGAGAAAUCA GAAGUUU	2131	5343-5365
AD-1397219.1	CUUCUGAUUUCUC UUCAGCUA	2042	5346-5366	UAGCTGAAGAGAAAUC AGAAGUU	2132	5344-5366
AD-1397220.1	CUGAUUUCUCUUC AGCUUUGA	2043	5349-5369	UCAAAGCUGAAGAGAA AUCAGAA	2133	5347-5369
AD-1397221.1	UGAUUUCUCUUCA GCUUUGAA	2044	5350-5370	UUCAAAGCUGAAGAGA AAUCAGA	2134	5348-5370
AD-1397222.1	GAUUUCUCUUCAG CUUUGAAA	2045	5351-5371	UTUCAAGCUGAAGAG AAUUCAG	2135	5349-5371
AD-1397223.1	ACUUGCAAGUCCC AUGAUUUA	2046	5460-5480	UAAATCAUGGGACUUG CAAGUGC	2136	5458-5480
AD-1397224.1	CUUGCAAGUCCCA UGAUUUCA	2047	5461-5481	UGAAAUCAUGGGACUU GCAAGUG	2137	5459-5481
AD-1397225.1	UGCAAGUCCCAUG AUUUCUUA	2048	5463-5483	UAAGAAAUCAUGGGAC UUGCAAG	2138	5461-5483
AD-1397226.1	CAAGUCCCAUGAU UUCUUCGA	2049	5465-5485	UCGAAGAAAUCAUGGG ACUUGCA	2139	5463-5485
AD-1397227.1	AGUCCCAUGAUUU CUUCGGUA	2050	5467-5487	UACCGAAGAAATCAUG GGACUUG	2140	5465-5487
AD-1397228.1	GUCCCAUGAUUUC UUCGGUAA	2051	5468-5488	UTACCGAAGAAAUCAU GGGACUU	2141	5466-5488
AD-1397229.1	UCCCAUGAUUUCU UCGGUAAA	2052	5469-5489	UTUACCGAAGAAAUCA UGGGACU	2142	5467-5489
AD-1397230.1	CCCAUGAUUUCUU CGGUAAUA	2053	5470-5490	UAUUACCGAAGAAAUC AUGGGAC	2143	5468-5490
AD-1397231.1	CCAUGAUUUCUUC GGUAAUUA	2054	5471-5491	UAAUTACCGAAGAAAU CAUGGGA	2144	5469-5491
AD-1397232.1	AGGGACAUGAAAU CAUCUUA	2055	5505-5525	UUAAGATGAUUUCAUG UCCUCC	2145	5503-5525

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910 .6
AD-1397233.1	GGGACAUGAAAUC AUCUUAGA	2056	5506-5526	UCUAAGAUGAUTUCAU GUCCCUC	2146	5504-5526
AD-1397234.1	GGACAUGAAAUCA UCUUAGCA	2057	5507-5527	UGCUAAGAUGATUUCA UGUCCCU	2147	5505-5527
AD-1397235.1	GACAUGAAAUCAU CUUAGCUA	2058	5508-5528	UAGCTAAGAUGAUUUC AUGUCCC	2148	5506-5528
AD-1397236.1	ACAUGAAAUCAUC UUAGCUUA	2059	5509-5529	UAAGCUAAGAUGAUUU CAUGUCC	2149	5507-5529
AD-1397237.1	AUGAAAUCAUCUU AGCUUAGA	2060	5511-5531	UCUAAGCUAAGAUGAU UUCAUGU	2150	5509-5531
AD-1397238.1	GAAAUCAUCUUAG CUUAGCUA	2061	5513-5533	UAGCTAAGCUAAGAUG AUUUCAU	2151	5511-5533
AD-1397239.1	AAAUCAUCUUAGC UUAGCUUA	2062	5514-5534	UAAGCUAAGCUAAGAU GAUUUCA	2152	5512-5534
AD-1397240.1	GUGAAUGUCUAUA UAGUGUAA	2063	5541-5561	UUACACTAUAUAGACA UUCACAG	2153	5539-5561
AD-1397241.1	AAUGUCUAUUAUAG UGUAUUGA	2064	5544-5564	UCAATACACUATAUAG ACAUUCA	2154	5542-5564
AD-1397242.1	UGUCUAUUAUAGUG UAUUGUGA	2065	5546-5566	UCACAATACACTAUAU AGACAUU	2155	5544-5566
AD-1397243.1	GUCUAUUAUAGUGU AUUGUGUA	2066	5547-5567	UACACAAUACACUAUA UAGACAU	2156	5545-5567
AD-1397244.1	UCUAUUAUAGUGUA UUGUGUGA	2067	5548-5568	UCACACAAUACACUAU AUAGACA	2157	5546-5568
AD-1397245.1	UAUAUAGUGUAUU GUGUGUUA	2068	5550-5570	UAACACACAAUACACU AUUAAGA	2158	5548-5570
AD-1397246.1	AUAUAGUGUAUUG UGUGUUUA	2069	5551-5571	UAAACACACAAUACAC UAUAUAG	2159	5549-5571
AD-1397247.1	CAAAUGAUUUACA CUGACUGA	2070	5574-5594	UCAGTCAGUGUAAAUC AUUUGUU	2160	5572-5594
AD-1397248.1	AAUGAUUUACACU GACUGUUA	2071	5576-5596	UAACAGTCAGUGUAAA UCAUUUG	2161	5574-5596
AD-1397249.1	GAAAUAAAGUUAU UACUCUGA	2072	5614-5634	UCAGAGTAAUAACUUU AUUUCCA	2162	5612-5634

Table 19. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 6

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397160.1	csasgag(Uhd)gaCfUfA fugauagugaaL96	2163	VPusdCsaudGedGagcud TgGfgucacgusgsa	2253	ACCAGAGUGACUA UGAUAGUGAA	2343
AD-1397161.1	gsgsacg(Chd)auGfUf AfucuuugaaauaL96	2164	VPusCfscadTg(C2p)gagc uuGfgGfucacgsusg	2254	AAGGACGCAUGUA UCUUGAAAUG	2344
AD-1397162.1	asesgca(Uhd)guAfUfC fuugaaaugcaL96	2165	VPusAfscedAu(G2p)cga gcuUfgGfgucacgsu	2255	GGACGCAUGUAUC UUGAAAUGCU	2345
AD-1397163.1	csgscau(Ghd)uaUfCfU fugaaaugcuL96	2166	VPusdGsacdCadTgagad GcUfugggucasesg	2256	GACGCAUGUAUCU UGAAAUGCUU	2346
AD-1397164.1	gscsaug(Uhd)auCfUf UfgaaaugcuuaL96	2167	VPusUfsgadCc(Agn)ugc gagCfuUfggucasc	2257	ACGCAUGUAUCUU GAAUGCUUG	2347
AD-1397165.1	csasugu(Ahd)ucUfUf GfaaaugcuugaL96	2168	VPusdCsugdAcdCaugcd GaGfcuuggguscsa	2258	CGCAUGUAUCUUG AAAUGCUUGU	2348
AD-1397166.1	usgsuau(Chd)uuGfAf AfaugcuuguaaL96	2169	VPusAfsudGa(C2p)cau gcgAfgCfuugggsusc	2259	CAUGUAUCUUGAA AUGCUUGUAA	2349

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397167.1	gsusauc(Uhd)ugAfAfAfugcuuguaaaL96	2170	VPusUfsacdTg(Agn)ccaugcGfaGfcuugsgsgsu	2260	AUGUAUCUUGAAAUGCUUGUAAA	2350
AD-1397168.1	csusuga(Ahd)auGfCfUfuguaagagaL96	2171	VPusUfsuadCu(G2p)accAugCfGfGfcuugsgsg	2261	AUCUUGAAAUGCUUGUAAAAGAGG	2351
AD-1397169.1	ususgaa(Ahd)ugCfUfUfguaaagaggaL96	2172	VPusUfsugdTa(G2p)acuauuUfgCfacacugsgc	2262	UCUUGAAAUGCUUGUAAAAGAGGU	2352
AD-1397170.1	usgsaaa(Uhd)gcUfUfGfuuaagagguaL96	2173	VPusUfsggdTu(Tgn)guagacUfaUfugcascsa	2263	CUUGAAAUGCUUGUAAAAGAGGUU	2353
AD-1397171.1	gsasaa(Ghd)cuUfGfUfaaagagguaL96	2174	VPusUfscadAc(Tgn)gguuugUfaGfacuaususu	2264	UUGAAAUGCUUGUAAAAGAGGUUU	2354
AD-1397172.1	asasaug(Chd)uuGfUfAfaagagguaL96	2175	VPusGfsgudCa(Agn)cugguUfGfagacuasasu	2265	UGAAAUGCUUGUAAAAGAGGUUUC	2355
AD-1397173.1	asasugc(Uhd)ugUfAfAfagagguaL96	2176	VPusAfsaggdTc(Agn)acugguUfuGfuagacsusa	2266	GAAAUGCUUGUAAAAGAGGUUUCU	2356
AD-1397174.1	asusgc(Uhd)guAfAfAfgagguaL96	2177	VPusGfsuudTa(Tgn)gauggaUfgUfugccusasa	2267	AAAUGCUUGUAAAAGAGGUUUCUA	2357
AD-1397175.1	usgscuu(Ghd)uaAfAfGfagguaL96	2178	VPusGfsgudTu(Agn)ugauggAfuGfuugccsusa	2268	AAUGCUUGUAAAAGAGGUUUCUAA	2358
AD-1397176.1	ususgua(Ahd)agAfGfGfuuaaaccL96	2179	VPusUfsggdTu(Tgn)augaugGfaUfguugcscsu	2269	GCUUGUAAAAGAGGUUUCUAAACCC	2359
AD-1397177.1	asusugc(Uhd)gcCfUfAfaagaaacuaL96	2180	VPusCfscudGg(Tgn)uuauaUfgGfauugsgsc	2270	ACAUUGCUGCCUAAGAAACUCA	2360
AD-1397178.1	usgscug(Chd)cuAfAfAfgaaacucagaL96	2181	VPusUfsgadAg(Tgn)caagcuUfcUfcagaususu	2271	AUUGCUGCCUAAAGAAACUCAGC	2361
AD-1397179.1	uscsugg(Uhd)uuGfGfGfuacaguaL96	2182	VPusAfsugCu(Agn)ccauguUfcGfagucgscsc	2272	CUUCUGGUUUGGUUACAGUAAAA	2362
AD-1397180.1	gsgsuuu(Ghd)ggUfAfCfaguuaaggaL96	2183	VPusdCsaadAudCcuuudGuUfcugccascsu	2273	CUGGUUUGGGUACAGUAAAAGGC	2363
AD-1397181.1	ususugg(Ghd)uaCfAfGfuuaaaggcaL96	2184	VPusdTscadAadTccuudTgUfugcugccsasc	2274	GGUUUGGGUACAGUAAAAGGCAA	2364
AD-1397182.1	gsasuuu(Ghd)guGfGfUfgguuagagaL96	2185	VPusGfsuudTc(Agn)aaucuuUfuGfuugcugsgc	2275	UAGAUUUGGUGGUUGGUUAGAGAU	2365
AD-1397183.1	usesauu(Ahd)cuGfCfCfaacaguuuaL96	2186	VPusAfsagdTu(Tgn)caauUcCfuUfugugcscsu	2276	CCUCAUACUGCCUAAACAGUUUCG	2366
AD-1397184.1	csasuuu(Chd)ugCfCfAfacaguucgaL96	2187	VPusdCsaadGudTucaadAuCfcuuugugsgsc	2277	CUCAUUACUGCCUACAGUUUCGG	2367
AD-1397185.1	usascug(Chd)caAfCfAfguuucggcuL96	2188	VPusdCscadAgdTuuuadAaUfcuuugusug	2278	AUUACUGCCUAAAGUUUCGGCUG	2368
AD-1397186.1	gsusucc(Uhd)cuUfCfCfugaaguucuaL96	2189	VPusdAscdaadGuuucdAaAfuccuuugususu	2279	CGGUUCCUCUUCUUGAAGUUCU	2369
AD-1397187.1	ususecu(Chd)uuCfCfUfagaaguucuaL96	2190	VPusdCsacdCadAguuudCaAfaucuuugsgsu	2280	GGUUCUUCUUCUUGAAGUUCUUG	2370
AD-1397188.1	usesuc(Uhd)ucCfUfGfaaguucugaL96	2191	VPusdAscdaadAaguudTcAfaauccuusug	2281	GUUCCUCUUCUUGAAGUUCUUGU	2371
AD-1397189.1	csesucu(Uhd)ccUfGfAfaaguucuaL96	2192	VPusAfsacdAc(Agn)ccaguUfuCfaaauccsu	2282	UUCUUCUUCUGAAGUUCUUGUG	2372
AD-1397190.1	csuscu(Chd)cuGfAfAfguuucuguaL96	2193	VPusCfsaadGg(Tgn)ugacauCfGfugccusug	2283	UCCUCUUCUGAAGUUCUUGUGC	2373
AD-1397191.1	usesuuc(Chd)ugAfAfGfuucugugcaL96	2194	VPusdAscdaadAgguudGaCfaucgucugsgc	2284	CCUCUUCUGAAGUUCUUGUGCC	2374
AD-1397192.1	csesage(Chd)uaAfGfAfucagguuaL96	2195	VPusAfsuudCa(C2p)acaggUfuGfacaucsgsu	2285	GGCCAGCCUAAAGUUCUUGUUA	2375
AD-1397193.1	asgscu(Chd)agAfUfCfaugguuagaL96	2196	VPusAfsaadCa(G2p)gguuucUfgUfggagcsasg	2286	CCAGCCUAAAGUUCUUGUUAAGG	2376
AD-1397194.1	gsescua(Chd)gaUfCfAfugguuaggaL96	2197	VPusUfsuudCa(Agn)ccuuaGfaAfcuaasusa	2287	CAGCCUAAAGUUCUUGUUAAGGG	2377

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397195.1	uscsagu(Ghd)cuGfGfCfagauaaauaL96	2198	VPusGfsuudCc(Agn)accuucAfgAfacucasasu	2288	GAUCAGUGCUGGCAGAUAAAUUG	2378
AD-1397196.1	csascgc(Uhd)ggCfUfUfugaucuuuaL96	2199	VPusdAsagdAgdAacugdGuUfagcccuasasa	2289	GGCACGCUGGCUUGUGAUCUUA	2379
AD-1397197.1	usgsgec(Uhd)agAfUfAfggauauacuaL96	2200	VPusdTscadCudAucaudAgUfcacucugsgsu	2290	GGUGGGCUAGAUAGGAUAUACUG	2380
AD-1397198.1	gsgegc(Uhd)gaUfAfGfgauauacugaL96	2201	VPusAfsuudTc(Agn)agauacAfuGfcgucesusu	2291	GUGGGCUAGAUAGGAUAUACUGU	2381
AD-1397199.1	csusaga(Uhd)agGfAfUfauacuguaaL96	2202	VPusGfscadTu(Tgn)caagauAfcAfugcguscsc	2292	GGCUAGAUAGGAUAUACUGUAUG	2382
AD-1397200.1	usasgau(Ahd)ggAfUfAfuacuguaugaL96	2203	VPusdAsgcdAudTucaadGaUfacaugcgscusc	2293	GCUAGAUAGGAUAUACUGUAUGC	2383
AD-1397201.1	ascsuca(Chd)uuUfAfUfcaauaguuaL96	2204	VPusAfsagdCa(Tgn)uucagaAfuAfcuugcgsgsu	2294	UGACUCACUUUAUCAAUAGUCC	2384
AD-1397202.1	csuscac(Uhd)uuAfUfCfaauaguuccaL96	2205	VPusCfsaadGc(Agn)uuucaaGfaUfacaugcgsg	2295	GACUCACUUUAUCAAUAGUCC	2385
AD-1397203.1	uscsacu(Uhd)uaUfCfAfauguuccaaL96	2206	VPusUfsacdAa(G2p)cauuucAfaGfauacasusg	2296	ACUCACUUUAUCAUAGUCCAU	2386
AD-1397204.1	csascuu(Uhd)auCfAfAfuaguuccauaL96	2207	VPusUfsuadCa(Agn)gcauuuCfaAfgauacsasu	2297	CUCACUUUAUCAUAGUCCAU	2387
AD-1397205.1	ascsuuu(Ahd)ucAfAfUfaguuccauuaL96	2208	VPusCsucdTudTacaadGcAfuuucaagsasu	2298	UCACUUUAUCAUAGUCCAUUU	2388
AD-1397206.1	asusagu(Uhd)ccAfUfUfuaaaauugacaL96	2209	VPusdCscudCudTuacadAgCfauuucaasgsa	2299	CAAUAGUCCAUUAUAAUUGACU	2389
AD-1397207.1	gsugsuga(Ghd)acUfGfUfauccuguuuaL96	2210	VPusAfsccdTc(Tgn)uuucaaGfcAfuuuucasasg	2300	GUGGUGAGACUGUAUCCUGUUUG	2390
AD-1397208.1	gsusgag(Ahd)cuGfUfAfuuccuguuugaL96	2211	VPusAfsacdCu(C2p)uuuacaAfgCfauuucsasa	2301	UGGUGAGACUGUAUCCUGUUUGC	2391
AD-1397209.1	usgsaga(Chd)ugUfAfUfcuguuugcaL96	2212	VPusAfsaadCc(Tgn)cuuuacAfaGfcauuuucsasa	2302	GGUGAGACUGUAUCCUGUUUGCU	2392
AD-1397210.1	gsasgac(Uhd)guAfUfCfcuguuugcuaL96	2213	VPusGfsaadAc(C2p)ucuuuaCfaAfgcauuususc	2303	GUGAGACUGUAUCCUGUUUGCUA	2393
AD-1397211.1	asgsacu(Ghd)uaUfCfCfuguuuugcuaL96	2214	VPusdAsgadAadCcucudTuAfcagaucsususu	2304	UGAGACUGUAUCCUGUUUGCUAU	2394
AD-1397212.1	csusgua(Uhd)ccUfGfUfuuugcuaugaL96	2215	VPusdTsgadAadAccucdTUfacaagcasusu	2305	GACUGUAUCCUGUAUUGCUAUUGC	2395
AD-1397213.1	usgsuau(Chd)cuGfUfUfugcuauugcaL96	2216	VPusGfsgudTa(G2p)aaaccuCfuUfuacaasgsc	2306	ACUGUAUCCUGUAUUGCUAUUGCU	2396
AD-1397214.1	gsusauc(Chd)ugUfUfUfgecuauugcuaL96	2217	VPusGfsagdTu(Tgn)cuuuagGfcAfgcauusgsu	2307	CUGUAUCCUGUAUUGCUAUUGCUU	2397
AD-1397215.1	usgsauu(Uhd)caAfCfCfacuuuugcuaL96	2218	VPusCfsugdAg(Tgn)uucuuuAfgGfcagcasasu	2308	CAUGAUUUCACACCACAUUUGCUA	2398
AD-1397216.1	usasugg(Ahd)caUfCfUfguuugcuuaL96	2219	VPusUfsuadAc(Tgn)guacccAfaAfcagcasasg	2309	AAUAUGGACAUCUGGUUUGCUUUG	2399
AD-1397217.1	asusgga(Chd)auCfUfGfuuugcuugaL96	2220	VPusdCscudTudAacugdTaCfcaaaacsasg	2310	AUAUGGACAUCUGGUUUGCUUUGG	2400
AD-1397218.1	asesuuc(Uhd)gaUfUfUfucuuucagcaL96	2221	VPusUfsgcdCu(Tgn)uaacugUfaCfcaaaascsc	2311	AAACUUCUGAUUUUCUCUUCAGCU	2401
AD-1397219.1	csusucu(Ghd)auUfUfCfucuuucagcaL96	2222	VPusdTscudCudAaccadCcAfccaaaucsa	2312	AACUUCUGAUUUUCUCUUCAGCUU	2402
AD-1397220.1	csusgau(Uhd)ucUfCfUfucagcuugaL96	2223	VPusGfsaadAc(Tgn)guuggcAfgUfaaugasgsg	2313	UUCUGAUUUCUCUUCAGCUUUGA	2403
AD-1397221.1	usgsauu(Uhd)cuCfUfUfcagcuugaL96	2224	VPusdCsgadAadCuguudGgCfaguuuagsasg	2314	UCUGAUUUCUCUUCAGCUUUGAA	2404
AD-1397222.1	gsasuuu(Chd)ucUfUfCfagcuuugaaaL96	2225	VPusdAsgedCgdAaacudGuUfggcaguasasu	2315	CUGAUUUCUCUUCAGCUUUGAAA	2405

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397223.1	ascsuug(Chd)aaGfUfCfcaugauuuuL96	2226	VPusAfsgadAc(Tgn)ucaggAfgAfggaacscsg	2316	GCACUUGCAAGUC CCAUGAUUUC	2406
AD-1397224.1	csusugc(Ahd)agUfCfCfcaugauuuuL96	2227	VPusdAsagdAadCuucadGgAfgagaggaascsc	2317	CACUUGCAAGUCC CAUGAUUUCU	2407
AD-1397225.1	usgscaa(Ghd)ucCfCfAfucauuuucuuL96	2228	VPusdCsaadGadAacuudAgGfaagaggasasc	2318	CUUGCAAGUCCCA UGAUUUCUUC	2408
AD-1397226.1	csasagu(Chd)ccAfUfGfauuucucgaL96	2229	VPusdAscAdAgdAacuudCaGfgaagaggsasa	2319	UGCAAAGUCCCAUG AUUUCUUCGG	2409
AD-1397227.1	asgsucc(Chd)auGfAfUfuucucgguaL96	2230	VPusdCsacdAadGaacudTcAfggaagagsgsa	2320	CAAGUCCCAUGAU UUCUUCGGUA	2410
AD-1397228.1	gsusccc(Ahd)ugAfUfUfucucgguaL96	2231	VPusdGscadCadAgaacdTuCfaggaagagsgsg	2321	AAGUCCCAUGAUU UCUUCGGUAA	2411
AD-1397229.1	uscseca(Uhd)gaUfUfUfucucgguaaL96	2232	VPusAfsaadCc(Agn)ugaucUfAfgcuggscsc	2322	AGUCCCAUGAUUU CUUCGGUAAU	2412
AD-1397230.1	csescan(Ghd)auUfUfCfucucgguaaL96	2233	VPusdCsuaadAadCcaugdAuCfuagagcugsgsg	2323	GUCCCAUGAUUUUC UUCGGUAAU	2413
AD-1397231.1	csesaug(Ahd)uuUfCfUfucgguaaL96	2234	VPusdCscudAadAccaudGaUfcuagagcsusg	2324	UCCCAUGAUUUUCU UCGGUAAUUC	2414
AD-1397232.1	asgsnga(Chd)auGfAfAfaucaucuuL96	2235	VPusdAsaudTudAucugdCcAfgcacugasusc	2325	GGAGGGACAUGAA AUCAUCUUAG	2415
AD-1397233.1	gsgsgac(Ahd)ugAfAfAfucacucuuagaL96	2236	VPusUfsaadGa(Tgn)cacagCfcAfgcgugscsc	2326	GAGGGACAUGAAA UCAUCUUAGC	2416
AD-1397234.1	gsgsaca(Uhd)gaAfAfUfcaucuuagcaL96	2237	VPusdAsgudAudAuccudAuCfuagccascsc	2327	AGGGACAUGAAAU CAUCUUAGCU	2417
AD-1397235.1	gsascau(Ghd)aaAfUfCfcaucuuagcaL96	2238	VPusdCsagdTadTaucdT aUfcuagcccsasc	2328	GGGACAUGAAAUC AUCUUAGCUU	2418
AD-1397236.1	ascsaug(Ahd)aaUfCfAfucauagcuuL96	2239	VPusAfsuadCa(G2p)uauaucCfuAfcuagscsc	2329	GGACAUGAAAUCA UCUUAGCUUA	2419
AD-1397237.1	asusgaa(Ahd)ucAfUfCfuuagcuuagaL96	2240	VPusdCsaudAcdAguaudAuCfcauacuasgsc	2330	ACAUGAAAUCAUC UUAGCUUAGC	2420
AD-1397238.1	gsasaa(Chd)auCfUfUfagcuuagcuL96	2241	VPusdGsaadCudAuugadTaAfgagaguscasa	2331	AUGAAAUCAUCUU AGCUUAGCUU	2421
AD-1397239.1	asasauc(Ahd)ucUfUfAfgcuuagcuuL96	2242	VPusGfsgadAc(Tgn)auu gauAfaAfgugagsusc	2332	UGAAAUCAUCUUA GCUUAGCUUU	2422
AD-1397240.1	gsusgaa(Uhd)guCfUfAfuaauagguuL96	2243	VPusUfsggdAa(C2p)uau ugaUfaAfgugagsgu	2333	CUGGAAUGUCUA UAUAUGUGUAU	2423
AD-1397241.1	asasugu(Chd)uaUfAfUfaguguauuagaL96	2244	VPusAfsugdGa(Agn)cua uugAfuAfaagugsasg	2334	UGAAUGUCUAUAU AGUGUAUUGU	2424
AD-1397242.1	usgsucu(Ahd)uaUfAfGfuguauugugaL96	2245	VPusAfsaudGg(Agn)acu auuGfaUfaagugsasa	2335	AAUGUCUAUAUAG UGUUAUUGUGU	2425
AD-1397243.1	gsuscua(Uhd)auAfGfUfguauuuguguaL96	2246	VPusdGsuedAadTuuaadAuGfgaacuausug	2336	AUGUCUAUAUAGU GUAUUGUGUG	2426
AD-1397244.1	uscuaau(Ahd)uaGfUfGfuauuuguguaL96	2247	VPusAfsaadCa(G2p)gau acaGfuCfucaccsasc	2337	UGUCUAUAUAGUG UAUUUGUGUGU	2427
AD-1397245.1	usasauu(Ahd)guGfUfAfuuguguguuL96	2248	VPusdCsaadAcdAggaudAcAfgucucacsasa	2338	UCUAUAUAGUGUA UUGUGUGUUU	2428
AD-1397246.1	asusaua(Ghd)ugUfAfUfuguguguuuL96	2249	VPusdGscadAadCaggadTaCfagucucascsc	2339	CUAUAUAGUGUAU UGUGUGUUUU	2429
AD-1397247.1	csasaa(Chd)auUfUfAfcacugacugaL96	2250	VPusdAsgcdAadAcaggdAuAfcagucucascsc	2340	AACAAAUGAUUUUA CACUGACUGU	2430
AD-1397248.1	asasuga(Uhd)uuAfCfAfcugacuguuL96	2251	VPusdTsgdCadAacagdGaUfacagucuscasa	2341	CAAAUGAUUUUACA CUGACUGUUG	2431
AD-1397249.1	gsasaa(Chd)aaGfUfUfauuacucugaL96	2252	VPusdCsaadTadGcaaadCaGfgauacagsusc	2342	UGGAAAUAUAAAGUU AUUACUCUGA	2432

Table 20. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 7

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910. 6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397070.2	ACGUGACCCAAGC UCGCAUGA	2433	512-532	UCAUGCGAGCUT GGGUCACGUGA	2521	510-532
AD-1397071.2	CGUGACCCAAGCU CGCAUGGA	2434	513-533	UCCATGCGAGCU UGGGUCACGUG	2522	511-533
AD-1397072.2	GUGACCCAAGCUC GCAUGGUA	2435	514-534	UACCAUGCGAGC UUGGGUCACGU	2523	512-534
AD-1397073.2	UGACCCAAGCUCG CAUGGUCA	2436	515-535	UGACCATGCGAG CUUGGGUCACG	2524	513-535
AD-1397074.2	GACCCAAGCUCGC AUGGUCAA	2437	516-536	UUGACCAUGC GA GCUUGGGUCAC	2525	514-536
AD-1397075.2	ACCCAAGCUCGCA UGGUCAGA	2438	517-537	UCUGACCAUGC G AGCUUGGGUCA	2526	515-537
AD-1397076.2	CCCAAGCUCGCAU GGUCAGUA	2439	518-538	UACUGACCAUGC GAGCUUGGGUC	2527	516-538
AD-1397077.2	CCAAGCUCGCAUG GUCAGUAA	2440	519-539	UUACTGACCAUG CGAGCUUGGGU	2528	517-539
AD-1397078.2	CAAGCUCGCAUGG UCAGUAAA	2441	520-540	UUUACUGACCAU GCGAGCUUGGG	2529	518-540
AD-1397250.1	AAGCUCGCAUGGU CAGUAAAA	2442	521-541	UUUUACTGACCA UGCGAGCUUGG	2530	519-541
AD-1397251.1	AGCUCGCAUGGUC AGUAAAAA	2443	522-542	UUUUTACUGACC AUGCGAGCUUG	2531	520-542
AD-1397252.1	GCUCGCAUGGUCA GUAAAAGA	2444	523-543	UCUUTUACUGAC CAUGCGAGCUU	2532	521-543
AD-1397253.1	CUCGCAUGGUCAG UAAAAGCA	2445	524-544	UGCUTUTACUGA CCAUGCGAGCU	2533	522-544
AD-1397254.1	UCGCAUGGUCAGU AAAAGCAA	2446	525-545	UUGCTUTUACUG ACCAUGCGAGC	2534	523-545
AD-1397255.1	CGCAUGGUCAGUA AAAGCAAA	2447	526-546	UUUGCUTUUACU GACCAUGCGAG	2535	524-546
AD-1397256.1	GCAUGGUCAGUA AAAGCAAAA	2448	527-547	UUUUGCTUUUAC UGACCAUGCGA	2536	525-547
AD-1397257.1	CAUGGUCAGUAA AAGCAAAGA	2449	528-548	UCUUTGCUUUUA CUGACCAUGC G	2537	526-548
AD-1397258.1	AUGGUCAGUAAA AGCAAAGAA	2450	529-549	UUCUTUGCUUUU ACUGACCAUGC	2538	527-549
AD-1397259.1	UGGUCAGUAAAA GCAAAGACA	2451	530-550	UGUCTUTGCUUU UACUGACCAUG	2539	528-550
AD-1397260.1	GGUCAGUAAAAG CAAAGACGA	2452	531-551	UCGUCUTUGCUU UUACUGACCAU	2540	529-551
AD-1397261.1	GUCAGUAAAAGC AAAGACGGA	2453	532-552	UCCGTCTUUGCTU UUACUGACCA	2541	530-552
AD-1397262.1	UCAGUAAAAGCA AAGACGGGA	2454	533-553	UCCCGUCUUUGC UUUUACUGACC	2542	531-553
AD-1397263.1	CAGUAAAAGCAA AGACGGGAA	2455	534-554	UTCCCGTCUUUGC UUUUACUGAC	2543	532-554
AD-1397264.1	AGUAAAAGCAAA GACGGGACA	2456	535-555	UGUCCCGUCUUU GCUUUUACUGA	2544	533-555
AD-1397265.1	GUAAAAGCAAAG ACGGGACUA	2457	536-556	UAGUCCCGUCUU UGCUIUUACUG	2545	534-556
AD-1397266.1	AUAUAUCAAAAC ACGUCCCGA	2458	1034-1054	UCGGGACGUGUT UGAUUAUAUCC	2546	1032-1054

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910. 6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397267.1	UAAUAUCAAACAC GUCCCGGA	2459	1035-1055	UCCGGGACGUGU UUGAUUUUAUC	2547	1033-1055
AD-1397268.1	AAUAUCAAACACG UCCCGGGA	2460	1036-1056	UCCCGGGACGUG UUUGAUUUUAU	2548	1034-1056
AD-1397269.1	AUAUCAAACACGU CCCGGGAA	2461	1037-1057	UUCCCGGGACGU GUUUGAUUUUA	2549	1035-1057
AD-1397270.1	UAUCAAACACGUC CCGGGAGA	2462	1038-1058	UCUCCCGGGACG UGUUUGAUUUU	2550	1036-1058
AD-1397271.1	AUCAAACACGUCC CGGGAGGA	2463	1039-1059	UCCUCCCGGGAC GUGUUUGAUUU	2551	1037-1059
AD-1397272.1	UCAAACACGUCCC GGGAGGCA	2464	1040-1060	UGCCTCCCGGGAC GUGUUUGAUA	2552	1038-1060
AD-1397273.1	CAAACACGUCCCG GGAGGCGA	2465	1041-1061	UCGCCUCCCGGG ACGUGUUUGAU	2553	1039-1061
AD-1397274.1	AAACACGUCCCGG GAGGCGGA	2466	1042-1062	UCCGCCTCCCGGG ACGUGUUUGA	2554	1040-1062
AD-1397275.1	AACACGUCCCGGG AGGCGGCA	2467	1043-1063	UGCCGCCUCCCG GGACGUGUUUG	2555	1041-1063
AD-1397276.1	ACACGUCCCGGGA GGCGGCAA	2468	1044-1064	UUGCCGCCUCCC GGGACGUGUUU	2556	1042-1064
AD-1397277.1	CACGUCCCGGGAG GCGGCAGA	2469	1045-1065	UCUGCCGCCUCCC GGGACGUGUU	2557	1043-1065
AD-1397278.1	ACGUCCCGGGAGG CGGCAGUA	2470	1046-1066	UACUGCCGCCUC CCGGGACGUGU	2558	1044-1066
AD-1397279.1	CGUCCCGGGAGGC GGCAGUGA	2471	1047-1067	UACTGCCGCCUC CCGGGACGUG	2559	1045-1067
AD-1397280.1	GUCCCGGGAGGCG GCAGUGUA	2472	1048-1068	UACACUGCCGCC UCCCGGGACGU	2560	1046-1068
AD-1397281.1	UCCCGGGAGGCGG CAGUGUGA	2473	1049-1069	UCACACTGCCGCC UCCCGGGACG	2561	1047-1069
AD-1397282.1	CCCGGGAGGCGGC AGUGUGCA	2474	1050-1070	UGCACACUGCCG CCUCCCGGGAC	2562	1048-1070
AD-1397283.1	CCGGGAGGCGGCA GUGUGCAA	2475	1051-1071	UUGCACACUGCC GCCUCCCGGGA	2563	1049-1071
AD-1397284.1	CGGGAGGCGGCAG UGUGCAAA	2476	1052-1072	UUUGCACACUGC CGCCUCCCGGG	2564	1050-1072
AD-1397285.1	GGGAGGCGGCAG UGUGCAAAA	2477	1053-1073	UUUUGCACACUG CCGCCUCCCGG	2565	1051-1073
AD-1397286.1	GGAGGCGGCAGU GUGCAAUA	2478	1054-1074	UAUUTGCACACU GCCGCCUCCCG	2566	1052-1074
AD-1397287.1	CAGUGUGCAAAU AGUCUACAA	2479	1062-1082	UUGUAGACUAUU UGCACACUGCC	2567	1060-1082
AD-1397079.2	AGUGUGCAAAUA GUCUACAAA	2480	1063-1083	UUUGTAGACUAU UUGCACACUGC	2568	1061-1083
AD-1397288.1	GUGUGCAAAUAG UCUACAAAA	2481	1064-1084	UUUUGUAGACUA UUUGCACACUG	2569	1062-1084
AD-1397289.1	UGUGCAAAUAGU CUACAAACA	2482	1065-1085	UGUUTGTAGACU AUUUGCACACU	2570	1063-1085
AD-1397290.1	GUGCAAAUAGUC UACAAACCA	2483	1066-1086	UGGUTUGUAGAC UAUUUGCACAC	2571	1064-1086
AD-1397080.2	UGCAAAUAGUCU ACAAACCAA	2484	1067-1087	UUGGTUTGUAGA CUAUUUGCACA	2572	1065-1087
AD-1397291.1	GCAAAUAGUCUAC AAACCAGA	2485	1068-1088	UCUGGUTUGUAG ACUAUUUGCAC	2573	1066-1088
AD-1397292.1	CAAAUAGUCUACA AACCAGUA	2486	1069-1089	UACUGGTUUGUA GACUAUUUGCA	2574	1067-1089

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910. 6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397293.1	AAAUAGUCUACA AACCAGUUA	2487	1070-1090	UAACTGGUUUGU AGACUAAUUGC	2575	1068-1090
AD-1397294.1	AAUAGUCUACAA ACCAGUUGA	2488	1071-1091	UCAACUGGUUUG UAGACUAAUUG	2576	1069-1091
AD-1397081.2	AUAGUCUACAAAC CAGUUGAA	2489	1072-1092	UUCAACTGGUUU GUAGACUAAU	2577	1070-1092
AD-1397295.1	UAGUCUACAAACC AGUUGACA	2490	1073-1093	UGUCAACUGGUT UGUAGACUAAU	2578	1071-1093
AD-1397082.2	AGUCUACAAACCA GUUGACCA	2491	1074-1094	UGGUCAACUGGU UUGUAGACUAAU	2579	1072-1094
AD-1397083.2	GUCUACAAACCAG UUGACCUA	2492	1075-1095	UAGGTCAACUGG UUUGUAGACUA	2580	1073-1095
AD-1397296.1	UCUACAAACCAGU UGACCUGA	2493	1076-1096	UCAGGUCAACUG GUUUGUAGACU	2581	1074-1096
AD-1397297.1	CUACAAACCAGUU GACCUGAA	2494	1077-1097	UUCAGGTCAACU GGUUUGUAGAC	2582	1075-1097
AD-1397298.1	UACAAACCAGUUG ACCUGAGA	2495	1078-1098	UCUCAGGUCAAC UGGUUUGUAGA	2583	1076-1098
AD-1397299.1	ACAAACCAGUUGA CCUGAGCA	2496	1079-1099	UGCUCAGGUCAA CUGGUUUGUAG	2584	1077-1099
AD-1397300.1	CAAACCAGUUGAC CUGAGCAA	2497	1080-1100	UUGCTCAGGUCA ACUGGUUUGUA	2585	1078-1100
AD-1397301.1	AAACCAGUUGACC UGAGCAAA	2498	1081-1101	UUUGCUCAGGUC AACUGGUUUGU	2586	1079-1101
AD-1397302.1	AACCAGUUGACCU GAGCAAGA	2499	1082-1102	UCUUGCTCAGGU CAACUGGUUUG	2587	1080-1102
AD-1397303.1	CAACAUCUCAU AAACCAGA	2500	1128-1148	UCUGGUTUAUGA UGGAUGUUGCC	2588	1126-1148
AD-1397087.2	AACAUCUCAUA AACCAGGA	2501	1129-1149	UCCUGGTUUAUG AUGGAUGUUGC	2589	1127-1149
AD-1397304.1	ACAUCUCAUAA ACCAGGAA	2502	1130-1150	UUCCTGGUUUAU GAUGGAUGUUG	2590	1128-1150
AD-1397305.1	CAUCCAUCUAAA CCAGGAGA	2503	1131-1151	UCUCCUGGUUUA UGAUGGAUGU	2591	1129-1151
AD-1397306.1	AUCCAUCUAAAC CAGGAGGA	2504	1132-1152	UCCUCCTGGUUTA UGAUGGAUGU	2592	1130-1152
AD-1397307.1	UCCAUCUAAACC AGGAGGUA	2505	1133-1153	UACCTCCUGGUU UAUGAUGGAUG	2593	1131-1153
AD-1397308.1	CCAUCAUAAACCA GGAGGUGA	2506	1134-1154	UCACCUCUGGUT UUAUGAUGGAU	2594	1132-1154
AD-1397309.1	CAUCAUAAACCAG GAGGUGGA	2507	1135-1155	UCCACCTCCUGGU UUAUGAUGGA	2595	1133-1155
AD-1397310.1	AUCAUAAACCAGG AGGUGGCA	2508	1136-1156	UGCCACCUCUG GUUUUAUGAUGG	2596	1134-1156
AD-1397311.1	UCAUAAACCAGGA GGUGGCCA	2509	1137-1157	UGGCCACCUCU GGUUUAUGAUG	2597	1135-1157
AD-1397312.1	CAUAAACCAGGAG GUGGCCAA	2510	1138-1158	UUGGCCACCUC UGGUUUAUGAU	2598	1136-1158
AD-1397313.1	AUAAACCAGGAG GUGGCCAGA	2511	1139-1159	UCUGGCCACCUC CUGGUUUAUGA	2599	1137-1159
AD-1397314.1	UAAACCAGGAGG UGGCCAGGA	2512	1140-1160	UCCUGGCCACCU CCUGGUUUAUG	2600	1138-1160
AD-1397315.1	AAACCAGGAGGU GGCCAGGUA	2513	1141-1161	UACCTGGCCACCU CCUGGUUUAU	2601	1139-1161
AD-1397316.1	AACCAGGAGGUG GCCAGGUGA	2514	1142-1162	UCACCUGGCCAC CUCCUGGUUUA	2602	1140-1162

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910. 6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1397317.1	ACCAGGAGGUGGC CAGGUGGA	2515	1143-1163	UCCACCTGGCCAC CUCCUGGUUU	2603	1141-1163
AD-1397318.1	CCAGGAGGUGGCC AGGUGGAA	2516	1144-1164	UUCCACCUGGCC ACCUCUGGUU	2604	1142-1164
AD-1397319.1	CAGGAGGUGGCCA GGUGGAAA	2517	1145-1165	UUUCCACCUGGC CACCUCUGGU	2605	1143-1165
AD-1397320.1	AGGAGGUGGCCA GGUGGAAGA	2518	1146-1166	UCUCCACCUGG CCACCUCUGG	2606	1144-1166
AD-1397321.1	GGAGGUGGCCAG GUGGAAGUA	2519	1147-1167	UACUTCCACCUG GCCACCUCUG	2607	1145-1167
AD-1397322.1	GAGGUGGCCAGG UGGAAGUAA	2520	1148-1168	UUACTUCCACCU GGCCACCUCU	2608	1146-1168

Table 21. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 7

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397070.2	ascsgug(Ahd)ccCfAfA fgcugcgaugL96	2609	VPusdCsaudGedGagcud TgGfgucacgsgsa	2697	UCACGUGACCCAA GCUCGCAUGG	2785
AD-1397071.2	csgsuga(Chd)ccAfAfG fcucgcaugL96	2610	VPusCfscadTg(C2p)gagc uuGfgGfucacgsg	2698	CACGUGACCCAAAG CUCGCAUGGU	2786
AD-1397072.2	gsusgac(Chd)caAfGfCf ucgcaugguaL96	2611	VPusAfsccdAu(G2p)cga gcuUfgGfgucacsgsu	2699	ACGUGACCCAAAGC UCGCAUGGUC	2787
AD-1397073.2	usgsacc(Chd)aaGfCfUf cgcaugguL96	2612	VPusdGsacdCadTgagad GcUfuggucacsg	2700	CGUGACCCAAAGCU CGCAUGGUCA	2788
AD-1397074.2	gsasccc(Ahd)agCfUfCf gcaugguL96	2613	VPusUfsgadCc(Agn)ugc gagCfuUfgggucsc	2701	GUGACCCAAAGCUC GCAUGGUCAG	2789
AD-1397075.2	ascscCa(Ahd)gcUfCfGf cauggucagL96	2614	VPusdCsugdAcCaugcd GaGfauuggguscsa	2702	UGACCCAAAGCUCG CAUGGUCAGU	2790
AD-1397076.2	csescaa(Ghd)cuCfGfCf auggucagL96	2615	VPusAfsccdGa(C2p)cau gcgAfgCfuugggsusc	2703	GACCCAAAGCUCGC AUGGUCAGUA	2791
AD-1397077.2	csesaag(Chd)ucGfCfAf uggucagL96	2616	VPusUfsacdTg(Agn)cca ugcGfGfauuggsgsu	2704	ACCCAAAGCUCGCA UGGUCAGUAA	2792
AD-1397078.2	csasagc(Uhd)cgCfAfUf ggucagL96	2617	VPusUfsuadCu(G2p)acc augCfGfGcuuggsgsg	2705	CCCAAGCUCGCAU GGUCAGUAAA	2793
AD-1397250.1	asasgcu(Chd)gcAfUfG fgucagL96	2618	VPusUfsuudAc(Tgn)gac cauGfGfagcuusgsg	2706	CCAAGCUCGCAUG GUCAGUAAAA	2794
AD-1397251.1	asgscuc(Ghd)caUfGfG fucagL96	2619	VPusUfsuudTa(C2p)uga ccaUfgCfGagcusug	2707	CAAGCUCGCAUGG UCAGUAAAAG	2795
AD-1397252.1	gsesucg(Chd)auGfGfU fcagL96	2620	VPusdCsuudTudAcugad CcAfugcgagcsusu	2708	AAGCUCGCAUGGU CAGUAAAAGC	2796
AD-1397253.1	csusegc(Ahd)ugGfUfC faguL96	2621	VPusdGscudTudTacugd AcCfaugcgagcsu	2709	AGCUCGCAUGGUC AGUAAAAGCA	2797
AD-1397254.1	usesgca(Uhd)ggUfCfA fguL96	2622	VPusUfsgcdTu(Tgn)uac ugaCfCfugcgagsgsc	2710	GCUCGCAUGGUCA GUAAAAGCAA	2798
AD-1397255.1	csgscAu(Ghd)guCfAfG fuL96	2623	VPusUfsugdCu(Tgn)uuu cugAfcCfaucgcsasg	2711	CUCGCAUGGUCAG UAAAAGCAAA	2799
AD-1397256.1	gsesaug(Ghd)ucAfGfU faaL96	2624	VPusUfsuudGc(Tgn)uuu acuGfGfcaugcsgsa	2712	UCGCAUGGUCAGU AAAAGCAAAG	2800
AD-1397257.1	csasugg(Uhd)caGfUfA faaL96	2625	VPusCfsuudTg(C2p)uuu uacUfgAfcgaugcsag	2713	CGCAUGGUCAGUA AAAGCAAAGA	2801
AD-1397258.1	asusggu(Chd)agUfAfA faaL96	2626	VPusUfscudTu(G2p)uuu uuuAfcGfcaugsgsc	2714	GCAUGGUCAGUAA AAGCAAAGAC	2802

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397259.1	usgsguc(Ahd)guAfAfA fagcaaagacaL96	2627	VPusGfsucdTu(Tgn)gcu uuuAfcUfgaccasusg	2715	CAUGGUCAGUAAA AGCAAAGACG	2803
AD-1397260.1	gsgsuca(Ghd)uaAfAfA fgcaaagacgaL96	2628	VPusCfsgudCu(Tgn)ugc uuuUfaCfugaccasasu	2716	AUGGUCAGUAAAA GCAAAGACGG	2804
AD-1397261.1	gsuscag(Uhd)aaAfAfG fcaaagacggaL96	2629	VPusdCscgdTedTuugcd TuUfuacugacsca	2717	UGGUCAGUAAAAG CAAAGACGGG	2805
AD-1397262.1	uscsagu(Ahd)aaAfGfC faaagacgggaL96	2630	VPusdCscgdGudCuugcd CuUfuacugacsca	2718	GGUCAGUAAAAGC AAAGACGGGA	2806
AD-1397263.1	csasgua(Ahd)aaGfCfAf aagacgggaL96	2631	VPusdTscgdCgdTcuuud GcUfuuuacugsasc	2719	GUCAGUAAAAGCA AAGACGGGAC	2807
AD-1397264.1	asgsuaa(Ahd)agCfAfA fagacgggacaL96	2632	VPusGfsucdCc(G2p)ucu uugCfuUfuacugsca	2720	UCAGUAAAAGCAA AGACGGGACU	2808
AD-1397265.1	gsusaaa(Ahd)gcAfAfA fgacgggacuaL96	2633	VPusAfsgudCc(C2p)guc uuuGfcUfuuuacsusg	2721	CAGUAAAAGCAAA GACGGGACUG	2809
AD-1397266.1	asusaau(Ahd)ucAfAfA fcacguccgaL96	2634	VPusdCsggdGadCgugud TuGfauuuuacsca	2722	GGAUAAUAUCAA CACGUCCCGG	2810
AD-1397267.1	usasaua(Uhd)caAfAfCf acgucccggaL96	2635	VPusCfscgdGg(Agn)cg uuUfgAfuuuacsca	2723	GAUAAUAUCAAAC ACGUCCCGGG	2811
AD-1397268.1	asasaau(Chd)aaAfCfAf cgucccggaL96	2636	VPusdCscgdGgdGacgud GuUfugauuuasasu	2724	AUAAUAUCAAACA CGUCCCGGGA	2812
AD-1397269.1	asusauc(Ahd)aaCfAfCf gucccggaL96	2637	VPusUfscgdCc(G2p)gac gugUfuUfgauuasusa	2725	UAUAUCAAACAC GUCCCGGGAG	2813
AD-1397270.1	usasuca(Ahd)acAfCfGf ucccggaL96	2638	VPusdCsudCedGggacd GuGfuuuuauasasu	2726	AAUAUCAAACACG UCCCGGGAGG	2814
AD-1397271.1	asuscaa(Ahd)caCfGfUf cccggaL96	2639	VPusdCsudCedCgggad CgUfuuuauasasu	2727	AUAUCAAACACGU CCCGGGAGGC	2815
AD-1397272.1	uscsaaa(Chd)acGfUfCf ccgggaggaL96	2640	VPusGfscgdTc(C2p)cg gacGfcUfuuuacsca	2728	UAUCAAACACGUC CCGGGAGGCG	2816
AD-1397273.1	csasaac(Ahd)cgUfCfCf cgggaggaL96	2641	VPusCfsgcdCu(C2p)ccg ggaCfcUfuuuacsca	2729	AUCAAACACGUCC CGGGAGGCGG	2817
AD-1397274.1	asasaca(Chd)guCfCfCf gggaggaL96	2642	VPusCfscgdCc(Tgn)ccc ggAfcGfuuuacsca	2730	UCAAAACACGUCCC GGGAGGCGGC	2818
AD-1397275.1	asascac(Ghd)ucCfCfGf ggagcggaL96	2643	VPusGfscgdGc(C2p)ucc cggGfaCfuuuacsca	2731	CAAACACGUCCCG GGAGGCGGCA	2819
AD-1397276.1	ascsacg(Uhd)ccCfGfGf gagcggaL96	2644	VPusUfscgdCc(C2p)cuc ccgGfcUfuuuacsca	2732	AAACACGUCCCGG GAGGCGGCAG	2820
AD-1397277.1	csasegu(Chd)ccGfGfGf aggcggaL96	2645	VPusdCsugdCedGccud CcGfggacgusasu	2733	AACACGUCCCGGG AGGCGGCAGU	2821
AD-1397278.1	ascsugc(Chd)cgGfGfA fgcgaggaL96	2646	VPusAfscudGc(C2p)gcc uccCfcGfggacgusasu	2734	ACACGUCCCGGGA GGCGGCAGUG	2822
AD-1397279.1	csgsucc(Chd)ggGfAfG fgcgaggaL96	2647	VPusCfsacdTg(C2p)cgcc ucCfcGfggacgusasu	2735	CACGUCCCGGGAG GGCGGCAGUGU	2823
AD-1397280.1	gsusccc(Ghd)ggAfGfG fcggcagugaL96	2648	VPusAfscadCu(G2p)ccg ccuCfcCfgggacgusasu	2736	ACGUCCCGGGAGG CGGCAGUGUG	2824
AD-1397281.1	uscsccg(Ghd)gaGfGfC fggcagugaL96	2649	VPusdCsacdAcdTgccgd CcUfcccgggacgusasu	2737	CGUCCCGGGAGGC GGCAGUGUGC	2825
AD-1397282.1	csescgg(Ghd)agGfCfG fgcagugcaL96	2650	VPusGfscadCa(C2p)ugc cgcCfuCfcccgggacgusasu	2738	GUCCCGGGAGGCG GCAGUGUGCA	2826
AD-1397283.1	csescgg(Ghd)ggCfGfG fcagugcaL96	2651	VPusUfscgdAc(Agn)cug ccgCfcUfcccgggacgusasu	2739	UCCCGGGAGGCGG CAGUGUGCAA	2827
AD-1397284.1	cssgga(Ghd)gcGfGfC fagugcaL96	2652	VPusUfsgudCa(C2p)acu gccGfcUfcccgggacgusasu	2740	CCCGGGAGGCGGC AGUGUGCAAA	2828
AD-1397285.1	gsgsgag(Ghd)cgGfCfA fgugcaL96	2653	VPusUfsgudGc(Agn)cac ugcCfcUfcccgggacgusasu	2741	CCGGGAGGCGGCA GUGUGCAAAU	2829
AD-1397286.1	gsgsagg(Chd)ggCfAfG fugcaL96	2654	VPusAfsuudTg(C2p)aca cugCfcGfcccgggacgusasu	2742	CGGGAGGCGGCAG UGUGCAAAUA	2830

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397287.1	csasgug(Uhd)gcAfAfAfuagucuacaaL96	2655	VPusUfsgudAg(Agn)cuauuuGfcAfcacugscsc	2743	GGCAGUGUGCAAAUAGUCUACAA	2831
AD-1397079.2	asgsugu(Ghd)caAfAfUfagucuacaaaL96	2656	VPusUfsgudTa(G2p)acuauuUfgCfacacugscsc	2744	GCAGUGUGCAAAUAGUCUACAA	2832
AD-1397288.1	gsusgug(Chd)aaAfUfAfgucuacaaaL96	2657	VPusUfsgudGu(Agn)gacuuuUfuGfcacacugscsc	2745	CAGUGUGCAAAUAUAGUCUACAA	2833
AD-1397289.1	usgsugc(Ahd)aaUfAfGfucuacaaaL96	2658	VPusUfsgudTg(Tgn)agacuaUfuUfgcacascsu	2746	AGUGUGCAAAUAGUCUACAA	2834
AD-1397290.1	gsusgca(Ahd)auAfGfUfcuacaaaccaL96	2659	VPusUfsgudTu(G2p)uagacuAfuUfgcacascsu	2747	GUGUGCAAAUAGUCUACAA	2835
AD-1397080.2	usgscaa(Ahd)uaGfUfcfuacaaaccaL96	2660	VPusUfsggdTu(Tgn)guagacUfaUfuugcacascsa	2748	UGUGCAAAUAGUCUACAA	2836
AD-1397291.1	gscsaaa(Uhd)agUfCfUfacaaccagaL96	2661	VPusUfsggdGudTugadGaCfuauuugcacascsa	2749	GUGCAAAUAGUCUACAA	2837
AD-1397292.1	csasaau(Ahd)guCfUfAfcacaccaguaL96	2662	VPusUfsggdGg(Tgn)uuguaGfUfauuugcacascsa	2750	UGCAAAUAGUCUACAA	2838
AD-1397293.1	asasaua(Ghd)ucUfAfCfcaaccaguuaL96	2663	VPusUfsggdTg(G2p)uuuguaGfUfauuugcacascsa	2751	GCAAAUAGUCUACAA	2839
AD-1397294.1	asasuag(Uhd)cuAfCfAfaaccaguuaL96	2664	VPusUfsggdCudGguuudGuAfgacuauuugcacascsa	2752	CAAAUAGUCUACAA	2840
AD-1397081.2	asusagu(Chd)uaCfAfAfaccaguugaaL96	2665	VPusUfsgcadAc(Tgn)gguuuGfUfGfauuugcacascsu	2753	AAAUAGUCUACAA	2841
AD-1397295.1	usasguc(Uhd)acAfAfAfcaccaguugacaL96	2666	VPusUfsgcadAadCuggdTuGfugacuauuugcacascsu	2754	AAUAGUCUACAA	2842
AD-1397082.2	asgsucu(Ahd)caAfAfCfcaccaguugacaL96	2667	VPusUfsgcadCa(Agn)cuguuUfgUfagacacacsc	2755	AUAGUCUACAA	2843
AD-1397083.2	gsuscuca(Chd)aaAfCfCfaguugaccuaL96	2668	VPusUfsgcadTc(Agn)acuguuUfgUfagacacacsc	2756	UAGUCUACAA	2844
AD-1397296.1	uscsuac(Ahd)aaCfCfAfcuugaccugaL96	2669	VPusUfsgcadGu(C2p)aacuggUfuUfguagacacsc	2757	AGUCUACAA	2845
AD-1397297.1	csusaca(Ahd)acCfAfGfGuugaccugaL96	2670	VPusUfsgcadGg(Tgn)caacugGfuUfugagacacsc	2758	GUCUACAA	2846
AD-1397298.1	usascaa(Ahd)ccAfGfUfugaccugagaL96	2671	VPusUfsgcadAg(G2p)ucaacuGfgUfugagacacsc	2759	UCUACAA	2847
AD-1397299.1	ascsaaa(Chd)caGfUfUfgaccugagcaL96	2672	VPusUfsgcadCa(G2p)gucaacUfgGfuugagacacsc	2760	CUACAA	2848
AD-1397300.1	csasaac(Chd)agUfUfGfaccugagcaL96	2673	VPusUfsgcadTc(Agn)ggucacCfuGfguuugagacacsc	2761	UACAA	2849
AD-1397301.1	asasacc(Ahd)guUfGfAfcugagagcaL96	2674	VPusUfsgcadCu(C2p)aggucaAfcUfguuugagacacsc	2762	ACAA	2850
AD-1397302.1	asascca(Ghd)uuGfAfCfcugagcaagaL96	2675	VPusUfsgcadGc(Tgn)cagguacAfaCfuguuugagacacsc	2763	CAACCAGUUGAC	2851
AD-1397303.1	csasaca(Uhd)ccAfUfCfauaaaccagaL96	2676	VPusUfsgcadGudTuauagdAuGfgauguuugagacacsc	2764	GGCAACAUCCAUC	2852
AD-1397087.2	asascau(Chd)caUfCfAfaaaaccagaL96	2677	VPusUfsgcadGg(Tgn)uuuugaUfgGfauuuugagacacsc	2765	GCAACAUCCAUC	2853
AD-1397304.1	ascsauc(Chd)auCfAfUfaaaccaggaaL96	2678	VPusUfsgcadTg(G2p)uuuauGfUfgauguuugagacacsc	2766	CAACAUCCAUC	2854
AD-1397305.1	csasucc(Ahd)ucAfUfAfaaaccaggagaL96	2679	VPusUfsgcadCu(G2p)guuuauGfUfgauguuugagacacsc	2767	AACAUCCAUC	2855
AD-1397306.1	asuscca(Uhd)caUfAfAfaaaccaggagaL96	2680	VPusUfsgcadCedTgguudTaUfgauguuugagacacsc	2768	ACAUCUCCAUC	2856
AD-1397307.1	uscscau(Chd)auAfAfAfaaaccaggagaL96	2681	VPusUfsgcadTc(C2p)ugguuuAfuGfauuuugagacacsc	2769	CAUCUCCAUC	2857
AD-1397308.1	cscsauc(Ahd)uaAfAfCfcaggaggagaL96	2682	VPusUfsgcadCudCuggdTuUfauuugagacacsc	2770	AUCCAUCUAAA	2858

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397309.1	csasuca(Uhd)aaAfCfCfaggagguggaL96	2683	VPusdCscadCcdTccugdGuUfuaugaugsgsa	2771	UCCAUCAUAAACCAGGAGGUGGCC	2859
AD-1397310.1	asuscau(Ahd)aaCfCfAfggagguggcaL96	2684	VPusGfscddAc(C2p)uccuggUfuUfaugausgsg	2772	CCAUCAUAAACCAAGGAGGUGGCC	2860
AD-1397311.1	uscsaua(Ahd)acCfAfGfgagguggccaL96	2685	VPusGfsgcdCa(C2p)cucGfuUfuaugasusg	2773	CAUCAUAAACCAGGAGGUGGCCA	2861
AD-1397312.1	csasuaa(Ahd)ccAfGfGfagguggccaL96	2686	VPusUfsggdCc(Agn)ccuGfGfUfuaugsasu	2774	AUCAUAAACCAGGAGGUGGCCAG	2862
AD-1397313.1	asusaaa(Chd)caGfGfAfgguggccaL96	2687	VPusCfsugdGc(C2p)accuccUfgGfuuausgsa	2775	UCAUAAACCAGGAGGUGGCCAGG	2863
AD-1397314.1	usasaac(Chd)agGfAfGfguggccaL96	2688	VPusCfsudGg(C2p)cacGfuGfuuuasusg	2776	CAUAAACCAGGAGGUGGCCAGGU	2864
AD-1397315.1	asasacc(Ahd)ggAfGfGfuggccaL96	2689	VPusAfscddTg(G2p)ccaccUcCfUfgguuasasu	2777	AUAAACCAGGAGGUGGCCAGGUG	2865
AD-1397316.1	asascca(Ghd)gaGfGfUfggccaL96	2690	VPusCfsacdCu(G2p)gccaccUfcCfugguusa	2778	UAAACCAGGAGGUGGCCAGGUGG	2866
AD-1397317.1	ascsag(Ghd)agGfUfGfaggagguggaL96	2691	VPusdCscadCcdTggccdAcCfuccuggususu	2779	AAACCAGGAGGUGGCCAGGUGGA	2867
AD-1397318.1	csasagg(Ahd)ggUfGfGfccagguggaaL96	2692	VPusUfscddAc(C2p)uggccaCfcUfcugggsusu	2780	AACCAGGAGGUGGCCAGGUGGAA	2868
AD-1397319.1	csasgga(Ghd)guGfGfCfcagguggaaaL96	2693	VPusUfsudCa(C2p)cuggccAfcCfuccugsgsu	2781	ACCAGGAGGUGGCCAGGUGGAAG	2869
AD-1397320.1	asgsag(Ghd)ugGfCfCffagguggaagaL96	2694	VPusCfsuudCc(Agn)ccuggcCfCfuccugsgsg	2782	CCAGGAGGUGGCCAGGUGGAAGU	2870
AD-1397321.1	gsasagg(Uhd)ggCfCfAfgguggaagaL96	2695	VPusAfscudTc(C2p)accuggCfcAfcuccusg	2783	CAGGAGGUGGCCAGGUGGAAGUA	2871
AD-1397322.1	gsasggu(Ghd)gcCfAfGfagguggaagaL96	2696	VPusUfsacdTu(C2p)caccuggGfcCfaccucscsu	2784	AGGAGGUGGCCAGGUGGAAGUAA	2872

Table 22. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 8

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1423242.1	GCAGAUAAUUAUAUAAGAAGCA	2873	975-995	UGCUTCTUAUUAUAUAUCUGCAC	2943	973-995
AD-1423243.1	CAGAUAAUUAUAUAAGAAGCUA	2874	976-996	UAGTUCUUAUTAAUUAUCUGCA	2944	974-996
AD-1423244.1	AGAUAAUUAUAUAAGAAGCUGA	2875	977-997	UCAGCUTCUAUUAUAUAUCUGC	2945	975-997
AD-1423245.1	GAUAAUUAUAUAAGAAGCUGGA	2876	978-998	UCCAGTUCUUAUAUAUAUCUG	2946	976-998
AD-1423246.1	AUAUUAUAUAUAAGAAGCUGGAA	2877	979-999	UTCCAGCUUCUTAUUAUUAUCU	2947	977-999
AD-1423247.1	UAAUUAUAUAUAAGAAGCUGGAUA	2878	980-1000	UAUCCAGCUUCTUAUAUUAUAUC	2948	978-1000
AD-1423248.1	AAUUAUAUAUAAGAAGCUGGAUCA	2879	981-1001	UGAUCCAGCUUCUUAUUAUAUAU	2949	979-1001
AD-1423249.1	AUUAUAUAUAAGAAGCUGGAUCUA	2880	982-1002	UAGATCCAGCUTCUAUUAUAUAUA	2950	980-1002
AD-1423250.1	UUAUAUAUAAGAAGCUGGAUCUUA	2881	983-1003	UAAGAUCCAGCTUCUUAUUAUAUAU	2951	981-1003
AD-1423251.1	UAAUAUAAGAAGCUGGAUCUUA	2882	984-1004	UTAAGATCCAGCUUAUUAUAUAU	2952	982-1004

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1423252.1	AAUAAGAAGCUGG AUCUUAGA	2883	985-1005	UCUAAGAUAUCCAGC UUCUUUUUAA	2953	983-1005
AD-1423253.1	AUAAGAAGCUGGA UCUUAGCA	2884	986-1006	UGCUAAGAUAUCCAG CUUCUUUUAA	2954	984-1006
AD-1423254.1	UAAGAAGCUGGAU CUUAGCAA	2885	987-1007	UTGCTAAGAUAUCCAG CUUCUUUUAA	2955	985-1007
AD-1423255.1	AAGAAGCUGGAUC UUAGCAAA	2886	988-1008	UTUGCUAAGAUAUCCAG GCUUCUUUUAA	2956	986-1008
AD-1423256.1	AGAAGCUGGAUCU UAGCAACA	2887	989-1009	UGUUGCTAAGATCC AGCUUCUUAA	2957	987-1009
AD-1423257.1	GAAGCUGGAUCUU AGCAACGA	2888	990-1010	UCGUTGCUAAGAUAUCCAG CAGCUUCUU	2958	988-1010
AD-1423258.1	AAGCUGGAUCUUA GCAACGUA	2889	991-1011	UACGTUGCUAAGAUAUCCAG CUUCUU	2959	989-1011
AD-1423259.1	AGCUGGAUCUUA CAACGUCA	2890	992-1012	UGACGUTGCUAAGAUAUCCAG CUUCUU	2960	990-1012
AD-1423260.1	GCUGGAUCUUA AACGUCCA	2891	993-1013	UGGACGTUGCUAAGAUAUCCAG CUUCUU	2961	991-1013
AD-1423261.1	CUGGAUCUUA ACGUCCAA	2892	994-1014	UTGGACGUUGCTAA GAUCCAGCU	2962	992-1014
AD-1423262.1	UGGAUCUUA CGUCCAGA	2893	995-1015	UCUGGACGUUGCUAAGAUAUCCAG CAGCU	2963	993-1015
AD-1423263.1	GGAUCUUA GUCCAGUA	2894	996-1016	UACUGGACGUUGCUAAGAUAUCCAG CAGCU	2964	994-1016
AD-1423264.1	GAUCUUA UCCAGUCA	2895	997-1017	UGACTGGACGUTGC UAAGAUAUCCAG	2965	995-1017
AD-1423265.1	AUCUUA CCAGUCCA	2896	998-1018	UGGACUGGACGTU GCUAAGAUAUCCAG	2966	996-1018
AD-1423266.1	UCUUA CAGUCCAA	2897	999-1019	UTGGACTGGACGUU GCUAAGAUAUCCAG	2967	997-1019
AD-1423267.1	CUUA AGUCCAAA	2898	1000-1020	UTUGGACUGGACG UUGCUAAGAUAUCCAG	2968	998-1020
AD-1423268.1	UUAGCA GUCCAAGA	2899	1001-1021	UCUUGGACUGGAC GUUGCUAAGAUAUCCAG	2969	999-1021
AD-1423269.1	UAGCA UCCAAGUA	2900	1002-1022	UACUTGGACUGGAC GUUGCUAAGAUAUCCAG	2970	1000-1022
AD-1423270.1	AGCA CCAAGUGA	2901	1003-1023	UACUTGGACUGGAC CGUUGCUAAGAUAUCCAG	2971	1001-1023
AD-1423271.1	GCAAC CAAGUGUA	2902	1004-1024	UACACUTGGACTGG ACGUUGCUAAGAUAUCCAG	2972	1002-1024
AD-1423272.1	CAAC AAGUGUGA	2903	1005-1025	UCACACTUGGACUG GACGUUGCUAAGAUAUCCAG	2973	1003-1025
AD-1423273.1	AACGU AGUGUGGA	2904	1006-1026	UCCACACUUGGACU GGACGUUGCUAAGAUAUCCAG	2974	1004-1026
AD-1423274.1	ACGU GUGUGGCA	2905	1007-1027	UGCCACACUUGGAC UGGACGUUGCUAAGAUAUCCAG	2975	1005-1027
AD-1423275.1	CGU UGUGGCUA	2906	1008-1028	UAGCCACACUUGG ACUGGACGUUGCUAAGAUAUCCAG	2976	1006-1028
AD-1423276.1	GUCC GUGGCUA	2907	1009-1029	UGAGCCACACUTGG ACUGGACGUUGCUAAGAUAUCCAG	2977	1007-1029
AD-1423277.1	UCCAG UGGCUCAA	2908	1010-1030	UTGAGCCACACTUG GACUGGACG	2978	1008-1030
AD-1423278.1	CCAGU GGCUCAA	2909	1011-1031	UTUGAGCCACACUU GGACUGGAC	2979	1009-1031
AD-1423279.1	CAGU GCUCAAAA	2910	1012-1032	UTUUGAGCCACACU UGGACUGGA	2980	1010-1032

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1423280.1	AGUCCAAGUGUGG CUCAAAGA	2911	1013-1033	UCUUTGAGCCACAC UUGGACUGG	2981	1011-1033
AD-1423281.1	GUCCAAGUGUGGC UCAAAGGA	2912	1014-1034	UCCUTUGAGCCACA CUUGGACUG	2982	1012-1034
AD-1423282.1	UCCAAGUGUGGCU CAAAGGAA	2913	1015-1035	UTCCTUTGAGCCAC ACUUGGACU	2983	1013-1035
AD-1423283.1	CCAAGUGUGGCUC AAAGGAUA	2914	1016-1036	UAUCCUTUGAGCCA CACUUGGAC	2984	1014-1036
AD-1423284.1	CAAGUGUGGCUCA AAGGAUAA	2915	1017-1037	UTAUCCTUUGAGCC ACACUUGGA	2985	1015-1037
AD-1423285.1	AAGUGUGGCUCAA AGGAUAAA	2916	1018-1038	UTUATCCUUUGAGC CACACUUGG	2986	1016-1038
AD-1423286.1	AGUGUGGCUCAAA GGAUAAUA	2917	1019-1039	UAUUAUCCUUUGA GCCACACUUG	2987	1017-1039
AD-1423287.1	GUGUGGCUCAAAG GAUAAUAA	2918	1020-1040	UTAUTATCCUUTGA GCCACACUU	2988	1018-1040
AD-1423288.1	UGUGGCUCAAAGG AUAAUAUA	2919	1021-1041	UAUATUAUCCUTUG AGCCACACU	2989	1019-1041
AD-1423289.1	GUGGCUCAAAGGA UAAUAUCA	2920	1022-1042	UGAUAUTAUCCTUU GAGCCACAC	2990	1020-1042
AD-1423290.1	UGGCUCAAAGGAU AAUAUCAA	2921	1023-1043	UTGATATUAUCCUU UGAGCCACA	2991	1021-1043
AD-1423291.1	GGCUCAAAGGAUA AUAUCAAA	2922	1024-1044	UTUGAUAUUAUCC UUUGAGCCAC	2992	1022-1044
AD-1423292.1	GCUCAAAGGAUAA UAUCAAAA	2923	1025-1045	UTUUGATAUUATCC UUUGAGCCA	2993	1023-1045
AD-1423293.1	CUCAAAGGAUAAU AUCAAACA	2924	1026-1046	UGUUTGAUUAUUAU CCUUUGAGCC	2994	1024-1046
AD-1423294.1	UCAAGGAUAAUA UCAACAA	2925	1027-1047	UTGUTUGAUAUTAU CCUUUGAGC	2995	1025-1047
AD-1423295.1	CAAAGGAUAAUAU CAAACACA	2926	1028-1048	UGUGTUTGAUTUA UCCUUUGAG	2996	1026-1048
AD-1423296.1	AAAGGAUAAUAUC AAACACGA	2927	1029-1049	UCGUGUTUGAUAU UAUCCUUUGA	2997	1027-1049
AD-1423297.1	AAGGAUAAUAUCA AACACGUA	2928	1030-1050	UACGTGTUUGATAU UAUCCUUUG	2998	1028-1050
AD-1423298.1	AGGAUAAUAUCAA ACACGUCA	2929	1031-1051	UGACGUGUUUGAU AUUAUCCUUU	2999	1029-1051
AD-1423299.1	GGAUAAUAUCAA CACGUCCA	2930	1032-1052	UGGACGTGUUUGA UAUUAUCCUU	3000	1030-1052
AD-1423300.1	GAUAAUAUCAAAC ACGUCCCA	2931	1033-1053	UGGGACGUGUUTG AUUAUAUCCU	3001	1031-1053
AD-1397266.2	AUAAUAUCAACA CGUCCCGA	2932	1034-1054	UCGGGACGUGUTU GAUAUUAUCC	3002	1032-1054
AD-1423301.1	UAAUAUCAAAACAC GUCCCGGA	2933	1035-1055	UCCGGGACGUGTUU GAUAUUAUC	3003	1033-1055
AD-1397268.2	AAUAUCAAAACACG UCCCGGGA	2934	1036-1056	UCCCGGACGUGU UUGAUUAUUAU	3004	1034-1056
AD-1423302.1	AUAUCAAAACACGU CCCGGGA	2935	1037-1057	UTCCCGGACGTGU UUGAUUAUA	3005	1035-1057
AD-1397270.2	UAUCAAAACACGUC CCGGGAGA	2936	1038-1058	UCUCCCGGACGUG UUUGAUUAU	3006	1036-1058
AD-1397271.2	AUCAAAACACGUCC CGGGAGGA	2937	1039-1059	UCCUCCCGGACGU GUUUGAUUAU	3007	1037-1059
AD-1423303.1	UCAAACACGUCCC GGGAGGCA	2938	1040-1060	UGCCTCCCGGACG UGUUUGAUA	3008	1038-1060

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1423304.1	CAAACACGUCCCG GGAGGCGA	2939	1041-1061	UCGCCUCCCGGGAC GUGUUUGAU	3009	1039-1061
AD-1423305.1	AAACACGUCCCGG GAGGCGGA	2940	1042-1062	UCCGCCTCCCGGGA CGUGUUUGA	3010	1040-1062
AD-1423306.1	AACACGUCCCGGG AGGCGGCA	2941	1043-1063	UGCCGCCUCCCGGG ACGUGUUUG	3011	1041-1063
AD-1397277.2	CACGUCCCGGGAG GCGGCAGA	2942	1045-1065	UCUGCCGCCUCCCG GGACGUGUU	3012	1043-1065

Table 23. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 8

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1423242.1	gsesaga(Uhd)aaUfUfA fauaagaagcaL96	3013	VPusdGscudTc(Tgn)uau udAaUfuaucugcsasc	3083	GUGCAGAUAAUUA AUAAGAAGCU	3153
AD-1423243.1	csasgau(Ahd)auUfAfA fuaagaagcuaL96	3014	VPusdAsgcdTu(C2p)uua udTaAfuaucugscsa	3084	UGCAGAUAAUUA UAAGAAGCUG	3154
AD-1423244.1	asgsaua(Ahd)uuAfAfU faagaagcugaL96	3015	VPusdCsgdCudTcuuad TuAfuaucugsc	3085	GCAGAUAAUUAU AAGAAGCUGG	3155
AD-1423245.1	gsasuaa(Uhd)uaAfUfA fagaagcuggaL96	3016	VPusdCscadGc(Tgn)ucu udAuUfuaucugsc	3086	CAGAUAAUUAU AGAAGCUGGA	3156
AD-1423246.1	asusaau(Uhd)aaUfAfA fagaagcuggaaL96	3017	VPusdTscdAg(C2p)uuc udTaUfuaucugsc	3087	AGAUAAUUAUUA GAAGCUGGAU	3157
AD-1423247.1	usasauu(Ahd)auAfAfG faagcuggauaL96	3018	VPusdAsudCa(G2p)cuu cdTuAfuaucugsc	3088	GAUAAUUAUUA AAGCUGGAUC	3158
AD-1423248.1	asasuua(Ahd)uaAfGfA fagcuggaucaL96	3019	VPusdGsaudCc(Agn)gcu udCuUfuaucugsc	3089	AUAAUUAUUA AGCUGGAUCU	3159
AD-1423249.1	asusuaa(Uhd)aaGfAfA fgcuggaucuaL96	3020	VPusdAsgadTc(C2p)agc udTcUfuaucugsc	3090	UAAUUAUUAAGAA GCUGGAUCUU	3160
AD-1423250.1	ususaau(Ahd)agAfAfG fcuggaucuaL96	3021	VPusdAsgdAudCcagcd TuCfuaucugsc	3091	AAUAAUUAAGAAG CUGGAUCUUA	3161
AD-1423251.1	usasaua(Ahd)gaAfGfC fuggaucuaL96	3022	VPusdTsaadGa(Tgn)cca gdCuUfuaucugsc	3092	AUAAUUAAGAAGC UGGAUCUUAAG	3162
AD-1423252.1	asasuaa(Ghd)aaGfCfUf ggaucuuaL96	3023	VPusdCsudAg(Agn)ucc adGcUfuaucugsc	3093	UUAUUAAGAAGCU GGAUCUUAAGC	3163
AD-1423253.1	asusaag(Ahd)agCfUfG fgaucuuaL96	3024	VPusdGscudAadGauced AgCfuaucugsc	3094	UAAUUAAGAAGCUG GAUCUUAAGCA	3164
AD-1423254.1	usasaga(Ahd)gcUfGfG faucuuagcaL96	3025	VPusdTsgcdTa(Agn)gau cdCaGfuaucugsc	3095	AAUUAAGAAGCUGG AUCUUAAGCAA	3165
AD-1423255.1	asasgaa(Ghd)cuGfGfA fucuuagcaL96	3026	VPusdTsgdCu(Agn)aga udCcAfuaucugsc	3096	AUAAGAAGCUGGA UCUUAAGCAAC	3166
AD-1423256.1	asgsaag(Chd)ugGfAfU fcuuagcaL96	3027	VPusdGsuudGc(Tgn)aag adTcCfuaucugsc	3097	UAAGAAGCUGGAU CUUAGCAACG	3167
AD-1423257.1	gsasagc(Uhd)ggAfUfC fuuagcaL96	3028	VPusdCsudTg(C2p)uua gdAuCfuaucugsc	3098	AAGAAGCUGGAUC UUAAGCAACGU	3168
AD-1423258.1	asasgcu(Ghd)gaUfCfU fuagcaL96	3029	VPusdAsgdTu(G2p)cua adGaUfuaucugsc	3099	AGAAGCUGGAUCU UAGCAACGUC	3169
AD-1423259.1	asgscug(Ghd)auCfUfU fagcaL96	3030	VPusdGsacdGudTgcuad AgAfuaucugsc	3100	GAAGCUGGAUCUU AGCAACGUCC	3170
AD-1423260.1	gsesugg(Ahd)ucUfUfA fgcaL96	3031	VPusdGsgadCgdTugcud AaGfuaucugsc	3101	AAGCUGGAUCUUA GCAACGUCCA	3171
AD-1423261.1	esugsga(Uhd)cuUfAfG fcaL96	3032	VPusdTsgdAc(G2p)uug cdTaAfuaucugsc	3102	AGCUGGAUCUUA CAACGUCCAG	3172
AD-1423262.1	usgsgau(Chd)uuAfGfC faL96	3033	VPusdCsugdGadCguugd CuAfuaucugsc	3103	GCUGGAUCUUAAGC AACGUCCAGU	3173

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1423263.1	gsgsauc(Uhd)uaGfCfA facguccaguaL96	3034	VPusdAscudGg(Agn)cg udGcUfaagaucscasg	3104	CUGGAUCUUAGCA ACGUCCAGUC	3174
AD-1423264.1	gsasucu(Uhd)agCfAfA fcguccagucaL96	3035	VPusdGsacdTg(G2p)acg udTgCfuaagaucscsa	3105	UGGAUCUUAGCAA CGUCCAGUCC	3175
AD-1423265.1	asuscuu(Ahd)gcAfAfC fguccaguccaL96	3036	VPusdGsgadCu(G2p)gac gdTuGfcuaagauscsc	3106	GGAUCUUAGCAAC GUCCAGUCCA	3176
AD-1423266.1	uscsuua(Ghd)caAfCfG fuccaguccaaL96	3037	VPusdTsggdAc(Tgn)gga cdGuUfgcuagaasusc	3107	GAUCUUAGCAACG UCCAGUCCAA	3177
AD-1423267.1	csusuag(CHd)aaCfGfUf ccaguccaaaL96	3038	VPusdTsgdGa(C2p)ugg adCgUfugcuagaasasu	3108	AUCUUAGCAACGU CCAGUCCAAG	3178
AD-1423268.1	ususagc(Ahd)acGfUfC fcaguccaagaL96	3039	VPusdCsuudGg(Agn)cug gdAcGfuuagcuasgsa	3109	UCUUAGCAACGUC CAGUCCAAGU	3179
AD-1423269.1	usasgca(Ahd)cgUfCfCf aguccaagualL96	3040	VPusdAscudTg(G2p)acu gdGaCfuuagcuasasg	3110	CUUAGCAACGUCC AGUCCAAGUG	3180
AD-1423270.1	asgscaa(CHd)guCfCfAf guccaagugaL96	3041	VPusdCsacdTu(G2p)gac udGgAfcguugcusasa	3111	UUAGCAACGUCCA GUCCAAGUGU	3181
AD-1423271.1	gscsaac(Ghd)ucCfAfGf uccaaguguaL96	3042	VPusdAscudCudTggacd TgGfacguugcsusa	3112	UAGCAACGUCCAG UCCAAGUGUG	3182
AD-1423272.1	csasagc(Uhd)ccAfGfUf ccaagugugaL96	3043	VPusdCsacdAcdTuggad CuGfgacguugscsu	3113	AGCAACGUCCAGU CCAAGUGUGG	3183
AD-1423273.1	asascgu(CHd)caGfUfCf caaguguggaL96	3044	VPusdCscadCadCuuggd AcUfggacguusgsc	3114	GCAACGUCCAGUC CAAGUGUGGC	3184
AD-1423274.1	ascsauc(CHd)agUfCfCf aaguguggaL96	3045	VPusdGscadAc(Agn)cuu gdGaCfuggacgusug	3115	CAACGUCCAGUCC AAGUGUGGCU	3185
AD-1423275.1	csgsucc(Ahd)guCfCfA faguguggcuaL96	3046	VPusdAsgcdCa(C2p)acu udGgAfcuggacgsusu	3116	AACGUCCAGUCCA AGUGUGGCUC	3186
AD-1423276.1	gsuscca(Ghd)ucCfAfA fuguggcucuaL96	3047	VPusdGsagdCc(Agn)cac udTgGfacuugcacsusu	3117	ACGUCCAGUCCAA GUGUGGCUCA	3187
AD-1423277.1	uscsagc(Uhd)ccAfAfG fuguggcucuaL96	3048	VPusdTsgadGc(C2p)aca cdTuGfgacuggascsg	3118	CGUCCAGUCCAAG UGUGGCUCUA	3188
AD-1423278.1	csesagu(CHd)caAfGfUf guggucuaaaL96	3049	VPusdTsgdAg(C2p)cac adCuUfggacuggsasc	3119	GUCCAGUCCAAGU GUGGCUCAAA	3189
AD-1423279.1	csasguc(CHd)aaGfUfGf uggucuaaaaL96	3050	VPusdTsuudGa(G2p)cca cdAcUfuggacugsgsa	3120	UCCAGUCCAAGUG UGGCUCAAAG	3190
AD-1423280.1	asgsucc(Ahd)agUfGfU fggcuaaagaL96	3051	VPusdCsuudTg(Agn)gcc adCaCfuuagcugsgsg	3121	CCAGUCCAAGUGU GGCUCAAAGG	3191
AD-1423281.1	gsuscca(Ahd)guGfUfG fgcuaaaggaaL96	3052	VPusdCscudTudGagccd AcAfcuuggacgsusg	3122	CAGUCCAAGUGUG GCUCAAAGGA	3192
AD-1423282.1	uscscaa(Ghd)ugUfGfG fcuaaaggaaL96	3053	VPusdTscdTuTgaged CaCfauuggasesu	3123	AGUCCAAGUGUGG CUCAAAGGAU	3193
AD-1423283.1	csesaag(Uhd)guGfGfC fuaaaggauaL96	3054	VPusdAsuedCudTugagd CcAfcacuuugsasc	3124	GUCCAAGUGUGGC UCAAAGGAUA	3194
AD-1423284.1	csasagu(Ghd)ugGfCfU fcaaaggauaaL96	3055	VPusdTsaudCc(Tgn)uug adGcCfcaacuugsgsa	3125	UCCAAGUGUGGCU CAAAGGAUAA	3195
AD-1423285.1	asasgug(Uhd)ggCfUfC faaaggauaaaL96	3056	VPusdTsuadTc(C2p)uuu gdAgCfcaacuugsgsg	3126	CCAAGUGUGGCUC AAAGGAUAAU	3196
AD-1423286.1	asgsugu(Ghd)gcUfCfA faaggauaauaL96	3057	VPusdAsuudAu(C2p)cuu udGaGfccacacusug	3127	CAAGUGUGGCUCA AAGGAUAAUA	3197
AD-1423287.1	gsusgug(Ghd)cuCfAfA faggauaauaaL96	3058	VPusdTsaudTa(Tgn)ccu udTgAfgccacacsusu	3128	AAGUGUGGCUCAA AGGAUAAUAU	3198
AD-1423288.1	usgsugg(CHd)ucAfAfA fggauaauaauL96	3059	VPusdAsuadTu(Agn)ucc udTuGfgaccacasesu	3129	AGUGUGGCUCAAA GGAUAAUAUC	3199
AD-1423289.1	gsusggc(Uhd)caAfAfG fgauaauaucaL96	3060	VPusdGsaudAudTaucd TuUfgagccacasesu	3130	GUGUGGCUCAAAG GAUAAUAUCA	3200
AD-1423290.1	usgsgeu(CHd)aaAfGfG fauaauaucaL96	3061	VPusdTsgadTa(Tgn)uau cdCuUfugagccacsa	3131	UGUGGCUCAAAGG AUAAUAUCAA	3201

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1423291.1	gsgscuc(Ahd)aaGfGfA fuaauaucaaaL96	3062	VPusdTsgdAudAuuaud CcUfuugagccsasc	3132	GUGGCUCAAAGGA UAAUAUCAA	3202
AD-1423292.1	gscsuca(Ahd)agGfAfU faauaucaaaL96	3063	VPusdTsuudGa(Tgn)auu adTcCfuugagcsca	3133	UGGCUCAAAGGAU AAUAUCAAAC	3203
AD-1423293.1	csuscaa(Ahd)ggAfUfA fauaucaaaL96	3064	VPusdGsuudTg(Agn)uau udAuCfcuuugagscsc	3134	GGCUCAAAGGAUA AUUAUCAAACA	3204
AD-1423294.1	uscsaaa(Ghd)gaUfAfA fuaucacaL96	3065	VPusdTsgudTu(G2p)aua udTaUfccuuugagsgc	3135	GCUCAAAGGAUAA UAUCAAACAC	3205
AD-1423295.1	csasaag(Ghd)auAfAfU faucaaacacaL96	3066	VPusdGsgudTu(Tgn)gau adTuAfuccuuugsasg	3136	CUCAAAGGAUAAU AUCAAACACG	3206
AD-1423296.1	asasagg(Ahd)uaAfUfA fuaaacacgaL96	3067	VPusdCsgudGu(Tgn)uga udAuUfuccuuusgsa	3137	UCAAGGAUAAUA UCAACACGUC	3207
AD-1423297.1	asasgga(Uhd)aaUfAfU fcaaacacgual96	3068	VPusdAscgdTg(Tgn)uug adTaUfuaucuuusug	3138	CAAAGGAUAAUAU CAAACACGUC	3208
AD-1423298.1	asgsgau(Ahd)auAfUfC faaacacgucaL96	3069	VPusdGsacdGu(G2p)uuu gdAuAfuaauccususu	3139	AAAGGAUAAUAUC AAACACGUCC	3209
AD-1423299.1	gsgsaau(Ahd)uaUfCfA faacacguccaL96	3070	VPusdGsgadCgdTguuud GaUfuaauccususu	3140	AAGGAUAAUAUCA AACACGUCCC	3210
AD-1423300.1	gsasuaa(Uhd)auCfAfA facacguccaL96	3071	VPusdGsggdAc(G2p)ug uudTgAfuaauuacsusu	3141	AGGAUAAUAUCAA ACACGUCCCC	3211
AD-1397266.2	asusaau(Ahd)ucAfAfA fcacgucccgaL96	3072	VPusdCsggdGadCgugud TuGfuaauuauuscsc	3142	GGAUAAUAUCAA CACGUCCCCG	3212
AD-1423301.1	usasaua(Uhd)caAfAfCf acgucccgaL96	3073	VPusdCscgdGg(Agn)cg gdTuUfgauuuuasc	3143	GAUAAUAUCAAAC ACGUCCCCGG	3213
AD-1397268.2	asasaau(Chd)aaAfCfAf cgucccggaL96	3074	VPusdCscgdGgdGacgud GuUfgauuuuasu	3144	AUAUAUCAAACA CGUCCCCGGA	3214
AD-1423302.1	asusauc(Ahd)aaCfAfCf gucccggaL96	3075	VPusdTscgdCg(G2p)gac gdTgUfgauuuuasu	3145	UAAUAUCAAACAC GUCCCCGAG	3215
AD-1397270.2	usasuaa(Ahd)acAfCfGf ucccggaL96	3076	VPusdCsucdCedGggacd GuGfuuuuauasu	3146	AAUAUCAAACACG UCCCCGGAGG	3216
AD-1397271.2	asuscaa(Ahd)caCfGfUf cccggaL96	3077	VPusdCscudCedCgggad CgUfguuuugausasu	3147	AUAUCAAACACGU CCCCGGAGGC	3217
AD-1423303.1	usesaaa(Chd)acGfUfCf ccgggaggaL96	3078	VPusdGscgdTc(C2p)egg gdAcGfuuuugausasu	3148	UAUCAAACACGUC CCGGGAGGCG	3218
AD-1423304.1	csasaac(Ahd)cgUfCfCf cgggaggaL96	3079	VPusdCsgcdCu(C2p)ccg gdGaCfuuuugausasu	3149	AUCAAACACGUCC CGGGAGGCGG	3219
AD-1423305.1	asasaca(Chd)guCfCfCf gggaggaL96	3080	VPusdCscgdCc(Tgn)ccc gdGgAfcguguuugsasu	3150	UCAACACGUCCCC GGGAGGCGGC	3220
AD-1423306.1	asascac(Ghd)ucCfCfGf ggaggaL96	3081	VPusdGscgdGc(C2p)ucc cdGgGfaguguuugsasu	3151	CAAACACGUCCCC GGAGGCGGCA	3221
AD-1397277.2	csasegu(Chd)ccGfGfGf aggcggaL96	3082	VPusdCsugdCedGccucd CcGfggagugususu	3152	AACACGUCCCCGG AGGCGGCAGU	3222

Table 24. MAPT Single Dose Screens in BE(2)C Cells-Screens 5-8

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397070.1	29	4	37	18	76	4
AD-1397070.2	35	2	48	6	45	7
AD-1397071.1	28	6	44	9	84	10

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397071.2	41	6	54	12	50	5
AD-1397072.1	12	3	16	2	44	3
AD-1397072.2	19	3	24	7	25	8
AD-1397073.1	20	10	26	4	79	4
AD-1397073.2	25	2	30	5	30	5
AD-1397074.1	52	14	55	12	93	16
AD-1397074.2	53	4	73	17	67	17
AD-1397075.1	47	10	59	25	80	4
AD-1397075.2	56	5	63	9	48	4
AD-1397076.1	16	6	29	10	65	5
AD-1397076.2	21	4	29	3	39	5
AD-1397077.1	17	6	24	5	79	13
AD-1397077.2	20	2	33	5	44	7
AD-1397078.1	22	5	28	7	75	13
AD-1397078.2	34	8	36	8	52	16
AD-1397250.1	75	10	69	11	76	18
AD-1397251.1	15	3	37	21	24	8
AD-1397252.1	24	6	24	7	35	12
AD-1397253.1	31	5	56	5	69	23
AD-1397254.1	40	8	41	2	49	9
AD-1397255.1	36	17	40	17	49	10
AD-1397256.1	53	7	65	11	75	15
AD-1397257.1	19	5	25	11	30	18
AD-1397258.1	17	2	24	6	32	11
AD-1397259.1	22	6	26	3	32	9
AD-1397260.1	41	11	54	10	75	11
AD-1397261.1	35	12	34	13	65	19
AD-1397262.1	34	16	44	19	45	10
AD-1397263.1	23	4	29	4	86	23
AD-1397264.1	27	7	26	3	58	15
AD-1397265.1	52	13	56	13	85	11
AD-1423242.1	130	30	96	27	84	15
AD-1423243.1	76	17	89	20	90	20
AD-1423244.1	85	8	90	26	90	10
AD-1423245.1	86	23	79	15	86	9
AD-1423246.1	83	8	85	27	83	10
AD-1423247.1	81	16	97	25	94	9
AD-1423248.1	90	21	84	24	91	16
AD-1423249.1	83	13	97	25	92	21
AD-1423250.1	88	19	85	24	92	11

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1423251.1	78	9	93	24	92	19
AD-1423252.1	81	14	94	22	94	20
AD-1423253.1	75	13	88	15	105	16
AD-1423254.1	90	10	104	27	97	20
AD-1423255.1	75	7	96	30	89	16
AD-1423256.1	130	34	126	33	149	34
AD-1423257.1	105	21	104	28	90	12
AD-1423258.1	89	19	105	33	89	20
AD-1423259.1	69	14	78	13	84	18
AD-1423260.1	78	10	93	27	86	17
AD-1423261.1	110	23	112	22	116	28
AD-1423262.1	115	39	117	37	94	22
AD-1423263.1	84	20	93	23	97	18
AD-1423264.1	97	25	95	20	98	23
AD-1423265.1	85	25	100	31	94	18
AD-1423266.1	95	15	107	29	95	21
AD-1423267.1	101	17	106	23	104	22
AD-1423268.1	102	29	115	30	110	23
AD-1423269.1	87	15	110	25	97	27
AD-1423270.1	117	36	133	31	118	36
AD-1423271.1	127	30	143	41	103	26
AD-1423272.1	98	26	89	23	109	28
AD-1423273.1	74	15	89	20	91	15
AD-1423274.1	89	12	92	20	98	17
AD-1423275.1	79	10	88	17	97	21
AD-1423276.1	92	20	102	13	120	27
AD-1423277.1	85	11	120	24	129	35
AD-1423278.1	38	7	79	10	114	21
AD-1423279.1	41	8	78	11	115	15
AD-1423280.1	89	21	96	28	99	23
AD-1423281.1	79	15	96	19	94	15
AD-1423282.1	79	13	86	12	103	18
AD-1423283.1	47	6	76	15	97	17
AD-1423284.1	62	8	91	17	113	18
AD-1423285.1	98	20	110	23	125	25
AD-1423286.1	121	28	133	27	152	16
AD-1423287.1	105	21	97	24	125	28
AD-1423288.1	86	17	89	14	92	11
AD-1423289.1	47	6	69	13	95	18
AD-1423290.1	91	18	89	25	99	23

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1423291.1	86	16	88	15	101	27
AD-1423292.1	110	22	109	18	130	29
AD-1423293.1	123	23	105	24	139	30
AD-1423294.1	159	19	132	22	130	33
AD-1423295.1	97	27	89	21	91	20
AD-1423296.1	75	13	89	22	83	7
AD-1423297.1	72	10	86	15	89	14
AD-1423298.1	69	10	91	20	84	6
AD-1423299.1	96	28	84	21	108	27
AD-1423300.1	93	24	93	19	105	24
AD-1397266.1	70		82	22	91	32
AD-1397266.2	94	10	104	16	113	21
AD-1397267.1	89	27	107	41	113	33
AD-1423301.1	131	18	112	27	135	33
AD-1397268.1	133	45	98	34	116	39
AD-1397268.2	87	17	95	20	108	20
AD-1397269.1	104	49	115	42	128	34
AD-1423302.1	85	13	98	19	102	13
AD-1397270.1	86	12	103	35	112	25
AD-1397270.2	99	19	94	19	92	19
AD-1397271.1	110	30	89	31	124	42
AD-1397271.2	84	16	106	25	108	18
AD-1397272.1	91	7	86	24	95	28
AD-1423303.1	93	18	111	24	102	16
AD-1397273.1	102	15	101	24	87	12
AD-1423304.1	108	24	124	32	123	23
AD-1397274.1	86	7	90	14	119	19
AD-1423305.1	114	19	135	14	136	16
AD-1397275.1	109	36	107	29	124	8
AD-1423306.1	72	10	95	26	82	13
AD-1397276.1	128	42	135	27	142	22
AD-1397277.1	137	29	117	30	131	17
AD-1397277.2	76	16	81	13	80	8
AD-1397278.1	166	21	156	33	167	24
AD-1397279.1	99	36	92	27	105	27
AD-1397280.1	99	21	80	13	87	6
AD-1397281.1	100	14	89	29	88	29
AD-1397282.1	104	25	99	17	80	19
AD-1397283.1	118	18	115	35	122	7
AD-1397284.1	120	24	118	37	133	20

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397285.1	175	25	161	32	151	37
AD-1397286.1	130	43	130	27	128	14
AD-1397287.1	79	11	72	20	91	19
AD-1397079.1	25	5	37	12	85	22
AD-1397079.2	34	6	46	17	58	12
AD-1397288.1	48	10	60	16	66	9
AD-1397289.1	57	16	46	10	52	12
AD-1397290.1	44	11	57	15	76	13
AD-1397080.1	12	5	14	3	77	12
AD-1397080.2	23	9	34	8	35	9
AD-1397291.1	33	5	46	14	61	11
AD-1397292.1	65	7	74	17	66	14
AD-1397293.1	17	3	20	4	22	3
AD-1397294.1	21	7	31	10	32	6
AD-1397081.1	14	4	19	7	67	15
AD-1397081.2	22	4	26	5	25	5
AD-1397295.1	18	4	34	10	40	10
AD-1397082.1	25	9	38	8	86	4
AD-1397082.2	49	13	50	12	62	20
AD-1397083.1	15	4	26	16	80	2
AD-1397083.2	31	6	50	7	63	20
AD-1397296.1	52	11	68	22	87	9
AD-1397297.1	28	8	42	9	60	13
AD-1397298.1	19	5	25	3	20	3
AD-1397299.1	18	5	27	5	34	9
AD-1397300.1	73	28	89	15	87	14
AD-1397301.1	51	12	49	15	61	19
AD-1397302.1	42	7	47	6	57	17
AD-1397084.1	18	6	26	4	100	20
AD-1397085.1	16	5	27	10	79	6
AD-1397086.1	65	12	62	16	85	5
AD-1397303.1	45	8	72	11	89	24
AD-1397087.1	18	5	31	7	90	11
AD-1397087.2	23	6	36	3	49	16
AD-1397304.1	33	3	36	6	38	2
AD-1397305.1	75	21	69	5	61	5
AD-1397306.1	28	6	41	3	44	10
AD-1397307.1	32	8	33	3	50	15
AD-1397308.1	33	7	44	10	51	14
AD-1397309.1	84	16	83	29	92	30

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397310.1	37	11	39	11	54	18
AD-1397311.1	63	18	64	10	60	11
AD-1397312.1	59	4	56	10	58	16
AD-1397313.1	72	11	55	5	60	16
AD-1397314.1	75	7	68	9	58	10
AD-1397315.1	30	11	40	8	52	22
AD-1397316.1	70	13	74	22	86	19
AD-1397317.1	111	4	130	12	99	32
AD-1397318.1	39	6	65	21	60	9
AD-1397319.1	43	29	37	7	42	6
AD-1397320.1	68	12	77	21	59	13
AD-1397321.1	81	17	74	18	63	14
AD-1397322.1	53	10	57	8	67	13
AD-1397088.1	11	3	13	2	62	2
AD-1397089.1	19	5	27	7	110	29
AD-1397090.1	54	15	42	13	73	15
AD-1397091.1	42	9	43	8	89	29
AD-1397092.1	41	12	44	11	105	2
AD-1397093.1	37	8	49	19	102	25
AD-1397094.1	43	9	40	14	74	6
AD-1397095.1	54	13	46	15	83	5
AD-1397096.1	54	13	63	27	84	13
AD-1397097.1	59	17	58	23	117	28
AD-1397098.1	52	15	44	16	96	23
AD-1397099.1	51	14	48	16	107	31
AD-1397101.1	50	12	39	7	73	11
AD-1397102.1	52	13	47	16	78	5
AD-1397103.1	56	16	54	22	92	16
AD-1397104.1	68	22	69	31	92	10
AD-1397105.1	72	20	68	33	111	18
AD-1397106.1	82	25	84	37	97	12
AD-1397107.1	75	28	78	38	86	4
AD-1397108.1	52	19	59	38	95	24
AD-1397109.1	48	2	45	24	81	11
AD-1397110.1	51	3	40	18	79	3
AD-1397111.1	63	6	63	35	98	8
AD-1397112.1	57	13	57	29	114	23
AD-1397113.1	57	5	59	36	113	19
AD-1397114.1	58	15	81	51	134	14
AD-1397115.1	80	15	85	33	121	17

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397116.1	65	16	63	26	82	11
AD-1397117.1	57	17	54	16	100	14
AD-1397118.1	64	15	68	24	98	21
AD-1397119.1	71	25	85	35	103	24
AD-1397120.1	73	20	75	32	118	28
AD-1397121.1	82	25	99	39	119	19
AD-1397122.1	81	24	89	28	156	17
AD-1397123.1	83	22	57	10	104	24
AD-1397124.1	73	20	59	16	89	5
AD-1397125.1	46	6	49	15	94	13
AD-1397126.1	55	13	46	12	81	2
AD-1397127.1	63	16	49	9	95	14
AD-1397128.1	78	22	56	25	87	13
AD-1397129.1	79	20	73	28	118	24
AD-1397130.1	86	29	81	42	116	24
AD-1397131.1	62	17	49	15	86	12
AD-1397132.1	46	10	42	18	73	8
AD-1397133.1	66	19	41	11	64	5
AD-1397134.1	47	12	51	16	83	12
AD-1397135.1	53	15	42	10	92	20
AD-1397136.1	54	16	52	13	106	30
AD-1397137.1	65	17	65	24	84	11
AD-1397138.1	39	10	33	7	62	15
AD-1397139.1	39	7	33	9	56	4
AD-1397140.1	44	13	57	23	79	31
AD-1397141.1	43	8	101	29	119	
AD-1397142.1	49	15	39	13	59	6
AD-1397143.1	45	14	38	14	52	3
AD-1397144.1	49	16	60	23	61	1
AD-1397145.1	50	14	36	11	52	2
AD-1397146.1	45	12	34	6	57	7
AD-1397147.1	42	13	38	14	61	1
AD-1397148.1	38	8	31	8	47	5
AD-1397149.1	42	13	37	14	54	3
AD-1397150.1	46	12	43	16	52	6
AD-1397151.1	52	16	57	29	80	13
AD-1397152.1	63	19	57	28	53	6
AD-1397153.1	43	12	37	13	79	9
AD-1397154.1	41	13	35	13	51	7
AD-1397155.1	39	10	30	5	50	4

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397156.1	43	8	37	9	66	10
AD-1397157.1	50	17	35	6	64	4
AD-1397158.1	51	14	41	16	57	8
AD-1397159.1	50	12	41	17	62	11
AD-1397160.1	55	12	54	10	61	7
AD-1397161.1	63	17	53	7	66	13
AD-1397162.1	52	11	53	11	56	4
AD-1397163.1	57	20	58	16	51	4
AD-1397164.1	60	21	45	4	57	5
AD-1397165.1	57	13	52	8	54	6
AD-1397166.1	44	6	46	6	52	7
AD-1397167.1	55	7	54	8	62	11
AD-1397168.1	57	17	55	10	65	15
AD-1397169.1	54	11	53	9	65	9
AD-1397170.1	63	13	58	13	77	17
AD-1397171.1	63	17	59	14	64	15
AD-1397172.1	61	20	53	10	57	7
AD-1397173.1	59	23	50	5	54	6
AD-1397174.1	51	8	57	18	82	13
AD-1397175.1	54	10	55	9	66	7
AD-1397176.1	52	7	54	11	71	19
AD-1397177.1	81	14	80	13	86	13
AD-1397178.1	76	10	76	8	85	6
AD-1397179.1	63	11	81	12	107	29
AD-1397180.1	68	16	93	30	134	37
AD-1397181.1	71	11	63	9	79	12
AD-1397182.1	64	16	65	12	91	18
AD-1397183.1	59	13	61	14	76	19
AD-1397184.1	53	10	56	8	76	11
AD-1397185.1	43	11	51	7	76	14
AD-1397186.1	77	23	63	12	82	19
AD-1397187.1	67	9	63	10	86	20
AD-1397188.1	70	21	72	25	80	20
AD-1397189.1	64	17	70	21	93	25
AD-1397190.1	47	17	55	11	69	11
AD-1397191.1	58	10	58	10	75	11
AD-1397192.1	65	13	72	10	89	10
AD-1397193.1	69	19	71	10	87	15
AD-1397194.1	93	22	91	16	102	11
AD-1397195.1	84	26	71	16	117	26

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397196.1	80	22	77	16	100	18
AD-1397197.1	91	13	101	21	146	35
AD-1397198.1	59	12	70	17	101	25
AD-1397199.1	56	8	57	8	79	13
AD-1397200.1	64	8	58	6	68	9
AD-1397201.1	57	8	51	8	64	11
AD-1397202.1	72	17	63	14	82	22
AD-1397203.1	69	22	62	11	86	19
AD-1397204.1	84	24	74	23	129	23
AD-1397205.1	82	16	82	16	123	17
AD-1397206.1	57	15	55	10	62	12
AD-1397207.1	56	9	64	10	88	13
AD-1397208.1	58	10	53	6	70	6
AD-1397209.1	58	11	60	10	75	12
AD-1397210.1	64	12	66	17	85	11
AD-1397211.1	71	17	73	17	90	24
AD-1397212.1	71	15	72	16	97	10
AD-1397213.1	56	19	52	10	73	20
AD-1397214.1	49	9	49	4	67	11
AD-1397215.1	51	8	56	13	68	11
AD-1397216.1	66	6	75	11	92	12
AD-1397217.1	71	9	81	17	98	15
AD-1397218.1	80	24	87	17	104	17
AD-1397219.1	61	19	71	13	98	18
AD-1397220.1	76	19	76	17	107	18
AD-1397221.1	54	12	62	15	79	16
AD-1397222.1	52	11	55	12	75	12
AD-1397223.1	58	12	63	16	84	19
AD-1397224.1	60	11	58	10	68	10
AD-1397225.1	61	15	55	11	68	11
AD-1397226.1	61	17	64	14	72	19
AD-1397227.1	66	15	72	16	84	22
AD-1397228.1	47	7	53	6	62	12
AD-1397229.1	49	9	48	8	53	4
AD-1397230.1	65	25	51	9	61	10
AD-1397231.1	67	26	57	16	61	5
AD-1397232.1	59	25	61	9	75	16
AD-1397233.1	61	15	66	17	93	27
AD-1397234.1	64	17	71	19	88	18
AD-1397235.1	61	19	56	11	90	23

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD	Avg % MAPT mRNA Remaining	SD
AD-1397236.1	47	11	49	7	57	6
AD-1397237.1	45	9	48	4	61	9
AD-1397238.1	46	7	48	9	51	4
AD-1397239.1	49	10	47	7	55	3
AD-1397240.1	49	11	48	10	68	18
AD-1397241.1	66	23	57	13	72	12
AD-1397242.1	64	15	69	17	91	22
AD-1397243.1	65	28	62	14	78	19
AD-1397244.1	52	20	42	5	64	31
AD-1397245.1	55	12	50	10	66	12
AD-1397246.1	46	12	49	10	54	8
AD-1397247.1	45	10	42	5	47	8
AD-1397248.1	52	13	50	10	55	11
AD-1397249.1	56	13	52	12	58	8

Table 25. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 9

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source	Range	Antisense Sequence 5' to 3'	SEQ ID NO:	Source	Range
AD-397167.1	UGGAAAUAAG UUAUUACUCA	3223	NM_001038609.2_5354-5374_s	5354-5374	UGAGUAAUAACU UUAUUUCCAAA	3252	NM_001038609.2_5352-5374_as	5352-5374
AD-393758.4	AGUGUGCAAU AGUCUACAAA	3224	NM_001038609.2_1065-1085_G21U_s	1065-1085	UUUGUAGACU UUGCACACUGC	3253	NM_001038609.2_1063-1085_C1A_as	1063-1085
AD-1397080.3	UGCAAAUAGUC UACAAACCAA	3225	NM_005910.6	1067-1087	UUGGTUTGUAGA CUAUUUGCACA	3254	NM_005910.6	1065-1087
AD-1397293.2	AAAUAGUCUAC AAACCAGUUA	3226	NM_005910.6	1070-1090	UAACTGGUUGU AGACUAAUUGC	3255	NM_005910.6	1068-1090
AD-1397294.2	AAUAGUCUACA AACCAGUUGA	3227	NM_005910.6	1071-1091	UCAACUGGUUG UAGACUAAUUG	3256	NM_005910.6	1069-1091
AD-1397081.3	AUAGUCUACAA ACCAGUUGAA	3228	NM_005910.6	1072-1092	UUCAACTGGUU GUAGACUAAUU	3257	NM_005910.6	1070-1092
AD-1397083.3	GUCUACAAACC AGUUGACCUA	3229	NM_005910.6	1075-1095	UAGGTCAACUGG UUUGUAGACUA	3258	NM_005910.6	1073-1095
AD-1397298.2	UACAAACCAGU UGACCUGAGA	3230	NM_005910.6	1078-1098	UCUCAGGUCAAC UGGUUUGUAGA	3259	NM_005910.6	1076-1098
AD-1397299.2	ACAAACCAGUU GACCUGAGCA	3231	NM_005910.6	1079-1099	UGCUCAGGUCAA CUGGUUUGUAG	3260	NM_005910.6	1077-1099
AD-1397084.2	AGGCAACAUC AUCAUAAACA	3232	NM_005910.6	1125-1145	UGUUTATGAUGG AUGUUGCCUAA	3261	NM_005910.6	1123-1145
AD-1397085.2	GGCAACAUCCA UCAUAAACCA	3233	NM_005910.6	1126-1146	UGGUTUAUGAUG GAUGUUGCCUA	3262	NM_005910.6	1124-1146
AD-1397087.3	AACAUCAUCA UAAACCAGGA	3234	NM_005910.6	1129-1149	UCCUGGTUUAUG AUGGAUGUUGC	3263	NM_005910.6	1127-1149

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Source	Range	Antisense Sequence 5' to 3'	SEQ ID NO:	Source	Range
AD-1397306.2	AUCCAUCAUAA ACCAGGAGGA	3235	NM_005910.6	1132-1152	UCCUCCTGGUUTA UGAUGGAUGU	3264	NM_005910.6	1130-1152
AD-1397307.2	UCCAUCAUAAA CCAGGAGGUA	3236	NM_005910.6	1133-1153	UACCTCCUGGUU UAUGAUGGAUG	3265	NM_005910.6	1131-1153
AD-1397308.2	CCAUCAUAAAC CAGGAGGUGA	3237	NM_005910.6	1134-1154	UCACCUCCUGGT UUAUGAUGGAU	3266	NM_005910.6	1132-1154
AD-1397088.2	AUCUGAGAAGC UUGACUUCAA	3238	NM_005910.6	1170-1190	UUGAAGTCAAGC UUCUCAGAUUU	3267	NM_005910.6	1168-1190
AD-523565.1	CGCAUGGUCAG UAAAAGCAAA	3239	NM_016841.4_524-544_A21U_s	524-544	UUUGCUIUUUACU GACCAUGCGAG	3268	NM_016841.4_522-544_U1A_as	522-544
AD-1397072.3	GUGACCCAAGC UCGCAUGGUA	3240	NM_005910.6	514-534	UACCAUGCGAGC UUGGGUCACGU	3269	NM_005910.6	512-534
AD-1397073.3	UGACCCAAGCU CGCAUGGUCA	3241	NM_005910.6	515-535	UGACCATGCGAG CUUGGGUCACG	3270	NM_005910.6	513-535
AD-1397076.3	CCAAGCUCGCG AUGGUCAGUA	3242	NM_005910.6	518-538	UACUGACCAUGC GAGCUUGGGUC	3271	NM_005910.6	516-538
AD-1397077.3	CCAAGCUCGCA UGGUCAGUAA	3243	NM_005910.6	519-539	UUACTGACCAUG CGAGCUUGGGU	3272	NM_005910.6	517-539
AD-1397078.3	CAAGCUCGCAU GGUCAGUAAA	3244	NM_005910.6	520-540	UUUACUGACCAU GCGAGCUUGGG	3273	NM_005910.6	518-540
AD-1397252.2	GCUCGCAUGGU CAGUAAAAGA	3245	NM_005910.6	523-543	UCUUTUACUGAC CAUGCGAGCUU	3274	NM_005910.6	521-543
AD-1397257.2	CAUGGUCAGUA AAAGCAAAAGA	3246	NM_005910.6	528-548	UCUUTGCUUUUA CUGACCAUGCG	3275	NM_005910.6	526-548
AD-1397258.2	AUGGUCAGUAA AAGCAAAGAA	3247	NM_005910.6	529-549	UUCUTUGCUUUU ACUGACCAUGC	3276	NM_005910.6	527-549
AD-1397259.2	UGGUCAGUAAA AGCAAAGACA	3248	NM_005910.6	530-550	UGUCTUTGCUUU UACUGACCAUG	3277	NM_005910.6	528-550
AD-1397263.2	CAGUAAAAGCA AAGACGGGAA	3249	NM_005910.6	534-554	UTCCCGTCUUUGC UUUUACUGAC	3278	NM_005910.6	532-554
AD-1397264.2	AGUAAAAGCAA AGACGGGACA	3250	NM_005910.6	535-555	UGUCCCGUCUUU GCUUUUACUGA	3279	NM_005910.6	533-555
AD-1397309.2	CAUCAUAAACC AGGAGGUGGA	3251	NM_005910.6	1135-1155	UCCACCTCCUGGU UUAUGAUGGA	3280	NM_005910.6	1133-1155

Table 26. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 9

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-397167.1	usgsgaaaUfaAfAfGfu auuacucaL96	3281	VPusGfsaguAfaUfAfacu uUfaUfuuccasasa	3310	UUUGGAAAUAAAG UUAUUACUCU	3339
AD-393758.4	asgsugugCfaAfAfUfag ucuacaaaL96	3282	VPusUfsuguAfgAfCfuau uUfgCfacacusgsc	3311	GCAGUGUGCAAU AGUCUACAAG	3340
AD-1397080.3	usgscaa(Ahd)uaGfUfC fuacaaaccaaL96	3283	VPusUfsggdTu(Tgn)gua gacUfaUfuucscasa	3312	UGUGCAAUAGUC UACAAACCAG	3341
AD-1397293.2	asasaua(Ghd)ucUfAfCf aaaccaguuaL96	3284	VPusAfsacdTg(G2p)uuu guaGfaCfuauusgsc	3313	GCAAUAGUCUAC AAACCAGUUG	3342
AD-1397294.2	asasuag(Uhd)cuAfCfA faaccaguugaL96	3285	VPusdCsaadCudGguuud GuAfgacuauusug	3314	CAAAUAGUCUACA AACCAGUUGA	3343
AD-1397081.3	asusagu(Chd)uaCfAfA faccaguugaL96	3286	VPusUfscadAc(Tgn)ggg uugUfaGfacuauusuu	3315	AAAUAGUCUACAA ACCAGUUGAC	3344
AD-1397083.3	gsuscua(Chd)aaAfCfCf aguugaccuaL96	3287	VPusAfsaggdTc(Agn)acu gggUfuGfuagacsusa	3316	UAGUCUACAAACC AGUUGACCUG	3345

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1397298.2	usasca(Ahd)ccAfGfUfugaccugagaL96	3288	VPusCfsucdAg(G2p)ucaacuGfgUfuuguasgsa	3317	UCUACAAACCAGUUGACCUGAGC	3346
AD-1397299.2	ascsaaa(Chd)caGfUfUfgaccugagcaL96	3289	VPusGfscudCa(G2p)gucaacUfgGfuugusasg	3318	CUACAAACCAGUUUGACCUGAGCA	3347
AD-1397084.2	asgsgea(Ahd)caUfCfCfaucauaaacaL96	3290	VPusGfsuudTa(Tgn)gauggaUfgUfugccusasa	3319	UUAGGCAACAUCUAUCAUAAAACC	3348
AD-1397085.2	gsagscaa(Chd)auCfCfAfucuaaaaccaL96	3291	VPusGfsgudTu(Agn)ugauggAfuGfuugccsusa	3320	UAGGCAACAUCCAUCAUAAAACCA	3349
AD-1397087.3	asascau(Chd)caUfCfAfuaaaccaggaL96	3292	VPusCfscudGg(Tgn)uuaugaUfgGfauguusgsc	3321	GCAACAUCCAUCAUAAACCAGGA	3350
AD-1397306.2	asuscca(Uhd)caUfAfAfaccaggaggaL96	3293	VPusdCscudCcdTgguudTaUfgauggausgsu	3322	ACAUCAUCAUAAACCAGGAGGU	3351
AD-1397307.2	uscscau(Chd)auAfAfAfccaggagguaL96	3294	VPusAfscddTc(C2p)ugguuuAfuGfauggasug	3323	CAUCAUCAUAAAACAGGAGGUG	3352
AD-1397308.2	csesauc(Ahd)uaAfAfCfcaggaggugaL96	3295	VPusdCsacdCudCcuugdTuUfaugauggsasu	3324	AUCAUCAUAAAACAGGAGGUGG	3353
AD-1397088.2	asuscug(Ahd)gaAfGfCfuugacuucalL96	3296	VPusUfsgadAg(Tgn)caagcuUfcUfcagaususu	3325	AAAUCUGAGAAGCUUGACUUCAA	3354
AD-523565.1	csgscaugGfuCfAfGfuaaagcaaaL96	3297	VPusUfsgucUfuUfUfucgAfcCfaugcgsasg	3326	CUCGCAUGGUCAGUAAAAGCAAA	3355
AD-1397072.3	gsusgac(Chd)caAfGfCfucgcaugguaL96	3298	VPusAfscddAu(G2p)cgaucuUfgGfgucacsgsu	3327	ACGUGACCCAAGCUCGCAUGGUC	3356
AD-1397073.3	usgsacc(Chd)aaGfCfUfcgcaugguaL96	3299	VPusdGsacdCadTgcegadGcUfugggucacscg	3328	CGUGACCCAAGCUCGCAUGGUC	3357
AD-1397076.3	csescaa(Ghd)cuCfGfCfauggucaguaL96	3300	VPusAfscudGa(C2p)caugcgAfgCfuugggsusc	3329	GACCCAAGCUCGC AUGGUCAGUA	3358
AD-1397077.3	csesaag(Chd)ucGfCfAfuuggucaguaL96	3301	VPusUfscadTg(Agn)ccaugcGfaGfcuuggsgsu	3330	ACCCAAGCUCGCAUGGUCAGUAA	3359
AD-1397078.3	csasagc(Uhd)cgCfAfUfaggucaguaL96	3302	VPusUfscudCu(G2p)accaugCfGfGcuuggsgsg	3331	CCCAAGCUCGCAUGGUCAGUAAA	3360
AD-1397252.2	gsesucg(Chd)auGfGfUfcaguaaaagaL96	3303	VPusdCsuudTudAcugadCcAfugcgagcsusu	3332	AAGCUCGCAUGGUCAGUAAAAGC	3361
AD-1397257.2	csasugg(Uhd)caGfUfAfaagcaaaagaL96	3304	VPusCfsuudTg(C2p)uuuuaUfgAfccaugscsg	3333	CGCAUGGUCAGUAAAGCAAAGA	3362
AD-1397258.2	asusguu(Chd)agUfAfAfaagcaaaagaL96	3305	VPusUfscudTu(G2p)cuuuuAfcUfGfaccusgsc	3334	GCAUGGUCAGUAAAGCAAAGAC	3363
AD-1397259.2	usgsugc(Ahd)guAfAfAfagcaaaagacaL96	3306	VPusGfsucdTu(Tgn)gcuuuuAfcUfgaccasusg	3335	CAUGGUCAGUAAAAGCAAAGACG	3364
AD-1397263.2	csasgua(Ahd)aaGfCfAfaagacgggaaL96	3307	VPusdTsccdCgdTcuuudGcUfuuuuacugsasc	3336	GUCAGUAAAAGCAAAGACGGGAC	3365
AD-1397264.2	asgsuaa(Ahd)agCfAfAfagacgggacaL96	3308	VPusGfsucdCe(G2p)ucuuugCfuUfuuuacusgsa	3337	UCAGUAAAAGCAAAGACGGGACU	3366
AD-1397309.2	csasuca(Uhd)aaAfCfCfaggagguggaL96	3309	VPusdCscadCcdTccugdGuUfuaugaugsgsa	3338	UCCAUCAUAAAACCAGGAGGUGGC	3367

Table 27. Unmodified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 10

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1566238	ACGUGACCCAAGCU CGCAUGA	3368	512-532	UCAUGCGAGCUUG GGUCACGUGA	3457	510-532
AD-1566239	CGUGACCCAAGCUC GCAUGGA	3369	513-533	UCCAUGCGAGCUU GGGUCACGUG	3458	511-533
AD-1566240	GUGACCCAAGCUCG CAUGGUA	3370	514-534	UACCAUGCGAGCU UGGGUCACGU	3459	512-534
AD-1566241	UGACCCAAGCUCGC AUGGUA	3371	515-535	UGACCAUGCGAGC UUGGGUCACG	3460	513-535
AD-1566242	GACCCAAGCUCGCA UGGUCAA	3372	516-536	UUGACCAUGCGAG CUUGGGUCAC	3461	514-536
AD-1566243	ACCCAAGCUCGCAU GGUCAGA	3373	517-537	UCUGACCAUGCGA GCUUGGGUCA	3462	515-537
AD-1566244	CCCAAGCUCGCAUG GUCAGUA	3374	518-538	UACUGACCAUGCG AGCUUGGGUC	3463	516-538
AD-1566245	CCAAGCUCGCAUGG UCAGUAA	3375	519-539	UUACUGACCAUGC GAGCUUGGGU	3464	517-539
AD-1566246	CAAGCUCGCAUGGU CAGUAAA	3376	520-540	UUUACUGACCAUG CGAGCUUGGG	3465	518-540
AD-1091965	AGCUCGCAUGGUCA GUAAAAA	3377	522-542	UUUUUACUGACCA UGCGAGCUUG	3466	520-542
AD-1566248	GCUCGCAUGGUCAG UAAAAA	3378	523-543	UCUUUUACUGACC AUGCGAGCUU	3467	521-543
AD-1566249	CUCGCAUGGUCAGU AAAAGCA	3379	524-544	UGCUUUUACUGAC CAUGCGAGCU	3468	522-544
AD-1566250	UCGCAUGGUCAGUA AAAGCAA	3380	525-545	UUGCUUUUACUGA CCAUGCGAGC	3469	523-545
AD-1091966	CGCAUGGUCAGUAA AAGCAAA	3381	526-546	UUUGCUUUUACUG ACCAUGCGAG	3470	524-546
AD-1566251	GCAUGGUCAGUAAA AGCAAAA	3382	527-547	UUUUGCUUUUACU GACCAUGCGA	3471	525-547
AD-1566252	CAUGGUCAGUAAAA GCAAAGA	3383	528-548	UCUUUGCUUUUAC UGACCAUGCG	3472	526-548
AD-1566253	AUGGUCAGUAAAAG CAAAGAA	3384	529-549	UUCUUUGCUUUUA CUGACCAUGC	3473	527-549
AD-1566254	UGGUCAGUAAAAGC AAAGACA	3385	530-550	UGUCUUUGCUUUU ACUGACCAUG	3474	528-550
AD-1566255	GGUCAGUAAAAGCA AAGACGA	3386	531-551	UCGUCUUUGCUUU UACUGACCAU	3475	529-551
AD-1566256	GUCAGUAAAAGCAA AGACGGA	3387	532-552	UCCGUCUUUGCUU UUACUGACCA	3476	530-552
AD-1566257	UCAGUAAAAGCAAA GACGGGA	3388	533-553	UCCCGUCUUUGCUU UUACUGACC	3477	531-553
AD-1566258	ACGUAAAAGCAAAG ACGGGAA	3389	534-554	UUCCCGUCUUUGCU UUUACUGAC	3478	532-554
AD-1566259	AGUAAAAGCAAAGA CGGGACA	3390	535-555	UGUCCCGUCUUUGC UUUUACUGA	3479	533-555
AD-692906	AGUGUGCAAUAGU CUACAAA	3391	1063-1083	UUUGUAGACUAUU UGCACACUGC	3480	1061-1083
AD-1566575	GUGCAAAUAGUCUA CAAACCA	3392	1066-1086	UGGUUUGUAGACU AUUUGCACAC	3481	1064-1086
AD-1566576	UGCAAAUAGUCUAC AAACCAA	3393	1067-1087	UUGGUUUGUAGAC UAUUUGCACA	3482	1065-1087
AD-1566577	GCAAAUAGUCUACA AACCAGA	3394	1068-1088	UCUGGUUUGUAGA CUAUUUGCAC	3483	1066-1088

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1566580	AAUAGUCUACAAAC CAGUUGA	3395	1071-1091	UCAACUGGUUUGU AGACUAAUUG	3484	1069-1091
AD-1566581	AUAGUCUACAAACC AGUUGAA	3396	1072-1092	UUCAACUGGUUUG UAGACUAAUU	3485	1070-1092
AD-1566582	UAGUCUACAAACCA GUUGACA	3397	1073-1093	UGUCAACUGGUUU GUAGACUAAU	3486	1071-1093
AD-1566583	AGUCUACAAACCAG UUGACCA	3398	1074-1094	UGGUCACUGGUU UGUAGACUAAU	3487	1072-1094
AD-1566584	GUCUACAAACCAGU UGACCUA	3399	1075-1095	UAGGUCACUGGU UUGUAGACUA	3488	1073-1095
AD-1566586	CUACAAACCAGUUG ACCUGAA	3400	1077-1097	UUCAGGUCAACUG GUUUGUAGAC	3489	1075-1097
AD-1566587	UACAAACCAGUUGA CCUGAGA	3401	1078-1098	UCUCAGGUCAACU GGUUUGUAGA	3490	1076-1098
AD-1566588	ACAAACCAGUUGAC CUGAGCA	3402	1079-1099	UGCUCAGGUCAAC UGGUUUGUAG	3491	1077-1099
AD-1566590	AAACCAGUUGACCU GAGCAAA	3403	1081-1101	UUUGCUCAGGUCA ACUGGUUUGU	3492	1079-1101
AD-1566591	AACCAGUUGACCUG AGCAAGA	3404	1082-1102	UCUUGCUCAGGUC AACUGGUUUG	3493	1080-1102
AD-1566634	AGGCAACAUCCAUC AUAACA	3405	1125-1145	UGUUUAUGAUGGA UGUUGCCUAA	3494	1123-1145
AD-1566635	GGCAACAUCCAUCA UAAACCA	3406	1126-1146	UGGUUUAUGAUGG AUGUUGCCUA	3495	1124-1146
AD-1566638	AACAUCAUCAUAA ACCAGGA	3407	1129-1149	UCCUGGUUUAUGA UGGAUGUUGC	3496	1127-1149
AD-1566639	ACAUCAUCAUAAA CCAGGAA	3408	1130-1150	UCCUGGUUUAUG AUGGAUGUUG	3497	1128-1150
AD-1566641	AUCCAUCAUAAACC AGGAGGA	3409	1132-1152	UCCUCCUGGUUUA UGAUGGAUGU	3498	1130-1152
AD-1566642	UCCAUCAUAAACCA GGAGGUA	3410	1133-1153	UACCUCCUGGUUU AUGAUGGAUG	3499	1131-1153
AD-1566643	CCAUCAUAAACCAG GAGGUGA	3411	1134-1154	UCACCUCCUGGUUU AUGAUGGAU	3500	1132-1154
AD-1566679	AUCUGAGAAGCUUG ACUUCAA	3412	1170-1190	UUGAAGUCAAGCU UCUCAGAUUU	3501	1168-1190
AD-1566861	CAGCAUCGACAUGG UAGACUA	3413	1395-1415	UAGUCUACCAUGU CGAUGCUGCC	3502	1393-1415
AD-1567153	UGGCAGCAACAAAG GAUUUGA	3414	1905-1925	UCAAUCCUUUGU UGCUGCCACU	3503	1903-1925
AD-1567154	GGCAGCAACAAAGG AUUUGAA	3415	1906-1926	UUCAAAUCCUUUG UUGCUGCCAC	3504	1904-1926
AD-1567157	AGCAACAAAGGAUU UGAAACA	3416	1909-1929	UGUUUCAAAUCCU UUGUUGCUGC	3505	1907-1929
AD-1567159	CAACAAAGGAUUUG AACUUA	3417	1911-1931	UAAGUUUCAAAUC CUUUGUUGCU	3506	1909-1931
AD-1567160	AACAAAGGAUUUGA AACUUGA	3418	1912-1932	UCAAGUUUCAAAU CCUUGUUGC	3507	1910-1932
AD-1567161	ACAAAGGAUUUGAA ACUUGGA	3419	1913-1933	UCCAAGUUUCAAA UCCUUGUUG	3508	1911-1933
AD-1567164	AAGGAUUUGAAACU UGGUGUA	3420	1916-1936	UACACCAAGUUUC AAAUCCUUUG	3509	1914-1936
AD-1567167	GAUUUGAAACUUGG UGUGUUA	3421	1919-1939	UAACACACCAAGU UUCAAAUCCU	3510	1917-1939
AD-1567199	GGCAGACGAUGUCA ACCUUGA	3422	1951-1971	UCAAGGUUGACAU CGUCUGCCUG	3511	1949-1971

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1567202	AGACGAUGUCAACC UUGUGUA	3423	1954-1974	UACACAAGGUUGA CAUCGUCUGC	3512	1952-1974
AD-1567550	GGCUAACCAGUUCU CUUUGUA	3424	2472-2492	UACAAAGAGAACU GGUUAGCCCU	3513	2470-2492
AD-1567554	AACCAGUUCUCUUU GUAAGGA	3425	2476-2496	UCCUUACAAAGAG AACUGGUUAG	3514	2474-2496
AD-1567784	UCUCAGUCCACUC AUCCAAA	3426	2828-2848	UUUGGAUGAGUGG AACUGAGAGU	3515	2826-2848
AD-1567896	UAGGUGUUUCUGCC UUGUUGA	3427	2943-2963	UCAACAAGGCAGA AACACCUAGG	3516	2941-2963
AD-1567897	AGGUGUUUCUGCCU UGUUGAA	3428	2944-2964	UUCAACAAGGCAG AAACACCUAG	3517	2942-2964
AD-1568105	AGCAGCUGAACAU UACAUA	3429	3277-3297	UUAUGUAUAUGUU CAGCUGCUC	3518	3275-3297
AD-1568108	AGCUGAACAUUAC AUAGAU	3430	3280-3300	UAUCUAUGUAUAU GUUCAGCUGC	3519	3278-3300
AD-1568109	GCUGAACAUUACA UAGAUGA	3431	3281-3301	UCAUCUAUGUAUA UGUUCAGCUG	3520	3279-3301
AD-1568139	GAGUUGUAGUUGGA UUUGUCA	3432	3331-3351	UGACAAAUCCAAC UACAACUCA	3521	3329-3351
AD-1568140	AGUUGUAGUUGGAU UUGUCUA	3433	3332-3352	UAGACAAAUCCAA CUACAACUCA	3522	3330-3352
AD-1568143	UGUAGUUGGAUUUG UCUGUUA	3434	3335-3355	UACAGACAAAUC CAACUACAAC	3523	3333-3355
AD-1568144	GUAGUUGGAUUUGU CUGUUUA	3435	3336-3356	UAAACAGACAAAU CCAACUACAA	3524	3334-3356
AD-1568148	UUGGAUUUGUCUGU UUAUGCA	3436	3340-3360	UGCAUAAACAGAC AAAUCCAACU	3525	3338-3360
AD-1568150	GGAUUUGUCUGUUU AUGCUUA	3437	3342-3362	UAAGCAUAAACAG ACAAAUCCA	3526	3340-3362
AD-1568151	GAUUUGUCUGUUUA UGCUUGA	3438	3343-3363	UCAAGCAUAAACA GACAAAUCCA	3527	3341-3363
AD-1568152	AUUUGUCUGUUUAU GCUUGGA	3439	3344-3364	UCCAAGCAUAAAC AGACAAAUCC	3528	3342-3364
AD-1568153	UUUGUCUGUUUAUG CUUGGAA	3440	3345-3365	UCCAAGCAUAAA CAGACAAAUC	3529	3343-3365
AD-1568154	UUGUCUGUUUAUGC UUGGAUA	3441	3346-3366	UAUCCAAGCAUAA ACAGACAAAU	3530	3344-3366
AD-1568158	CUGUUUAUGCUUGG AUUCACA	3442	3350-3370	UGUGAAUCCAAGC AUAAACAGAC	3531	3348-3370
AD-1568161	UUUAUGCUUGGAUU CACCAGA	3443	3353-3373	UCUGGUGAAUCCA AGCAUAAACA	3532	3351-3373
AD-1568172	AUUCACCAGAGUGA CUAUGAA	3444	3364-3384	UUCAUAGUCACUC UGGUGAAUCC	3533	3362-3384
AD-1568174	UCACCAGAGUGACU AUGAUAA	3445	3366-3386	UUAUCAUAGUCAC UCUGGUGAAU	3534	3364-3386
AD-1568175	CACCAGAGUGACUA UGAUAGA	3446	3367-3387	UCUAUCAUAGUCA CUCUGGUGAA	3535	3365-3387
AD-692908	ACCAGAGUGACUAU GAUAGUA	3447	3368-3388	UACUAUCAUAGUC ACUCUGGUGA	3536	3366-3388
AD-1568176	CCAGAGUGACUAUG AUAGUGA	3448	3369-3389	UCACUAUCAUAGU CACUCUGGUG	3537	3367-3389
AD-1569830	ACAUGAAAUCAUCU UAGCUUA	3449	5509-5529	UAAGCUAAGAUGA UUUCAUGUCC	3538	5507-5529
AD-1569832	AUGAAAUCAUCUUA GCUUAGA	3450	5511-5531	UCUAAGCUAAGAU GAUUUCAUGU	3539	5509-5531

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_005910.6
AD-1569834	GAAAUCAUCUUAGC UUAGCUA	3451	5513-5533	UAGCUAAGCUAAG AUGAUUUCAU	3540	5511-5533
AD-1569835	AAAUCAUCUUAGCU UAGCUUA	3452	5514-5534	UAAGCUAAGCUAA GAUGAUUUCA	3541	5512-5534
AD-1569862	GUGAAUGUCUAUUAU AGUGUAA	3453	5541-5561	UUACACUAUUAUAG ACAUUCACAG	3542	5539-5561
AD-1569872	AUAUAGUGUAUUGU GUGUUUA	3454	5551-5571	UAAACACACAAUA CACUAUUAUAG	3543	5549-5571
AD-1569890	CAAAUGAUUUACAC UGACUGA	3455	5574-5594	UCAGUCAGUGUAA AUCAUUUUGUU	3544	5572-5594
AD-1569892	AAUGAUUUACACUG ACUGUUA	3456	5576-5596	UACAGUCAGUGU AAAUCAUUUG	3545	5574-5596

Table 28. Modified Sense and Antisense Strand Sequences of MAPT dsRNA Agents- Screen 10

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1566238	ascsgug(Ahd)CfcCfAf Afgcucgcausgsa	3546	VPusCfsaugCfgAfGfcuu gGfgUfcacgusgsa	3635	UCACGUGACCCAA GCUCGCAUGG	1894
AD-1566239	csgsuga(Chd)CfcAfAf Gfcucgcausgsa	3547	VPusCfscuGfcGfAfgcu uGfgGfucacgusgsa	3636	CACGUGACCCAAG CUCGCAUGGU	1895
AD-1566240	gsusgac(Chd)CfaAfGf Cfucgcausgsa	3548	VPusAfsccaUfgCfGfage uUfgGfgucacgusu	3637	ACGUGACCCAAGC UCGCAUGGUC	1896
AD-1566241	usgsacc(Chd)AfaGfCf Ufcgcauggsusa	3549	VPusGfsaccAfuGfCfag cUfuGfgucacgscg	3638	CGUGACCCAAGCU CGCAUGGUCA	1897
AD-1566242	gsasccc(Ahd)AfgCfUf Cfcauggsusa	3550	VPusUfsgacCfaUfGfca gCfuUfggucgsa	3639	GUGACCCAAGCUC GCAUGGUCAG	1898
AD-1566243	asescca(Ahd)GfcUfCf Gfcauggsusa	3551	VPusCfsugaCfcAfUfgcg aGfcUfuggsusa	3640	UGACCCAAGCUCG CAUGGUCAGU	1899
AD-1566244	csescaa(Ghd)CfuCfGf Cfauggsusa	3552	VPusAfsugAfcCfAfgc gAfgCfuuggsusc	3641	GACCCAAGCUCGC AUGGUCAGUA	1900
AD-1566245	csesaag(Chd)UfcGfCf Afuggsusa	3553	VPusUfsacuGfaCfCfaug cGfaGfcuuggsusu	3642	ACCCAAGCUCGCA UGGUCAGUAA	1901
AD-1566246	csasagc(Uhd)CfGfCfAf Ufggucagusa	3554	VPusUfsuacUfgAfCfcau gCfGfAfgcuuggsug	3643	CCCAAGCUCGCAU GGUCAGUAAA	1902
AD-1091965	asgsucg(Ghd)CfaUfGf Gfucagaaasasa	3555	VPusUfsuuAfcUfGfacc aUfgCfagcuscusg	3644	CAAGCUCGCAUGG UCAGUAAAAG	740
AD-1566248	gsesucg(Chd)AfuGfGf Ufcaguaaaasgsa	3556	VPusCfsuuUfaCfUfgac cAfuGfcgagcsusu	3645	AAGCUCGCAUGGU CAGUAAAAGC	741
AD-1566249	csusgcg(Ahd)UfgGfUf Cfaguaaaagsusa	3557	VPusGfscuuUfuAfCfuga cCfaUfgcagcsusu	3646	AGCUCGCAUGGUC AGUAAAAGCA	2797
AD-1566250	uscsgea(Uhd)GfgUfCf Afguaaaagsusa	3558	VPusUfsgcuUfuUfAfcug aCfcAfgcaggsusc	3647	GCUCGCAUGGUCA GUAAAAGCAA	2798
AD-1091966	csgscau(Ghd)GfuCfAf Gfuaaaagcasasa	3559	VPusUfsgucUfuUfUfacu gAfcCfagcgsasg	3648	CUCGCAUGGUCAG UAAAAGCAA	1201
AD-1566251	gsesaug(Ghd)UfcAfGf Ufaaaagcaasasa	3560	VPusUfsuugCfuUfUfuac uGfaCfcaugcsusa	3649	UCGCAUGGUCAGU AAAAGCAAAG	2800
AD-1566252	csasugg(Uhd)CfaGfUf Afaaaagcaasgsa	3561	VPusCfsuuUfgUfUfuua cUfgAfcuagcsusc	3650	CGCAUGGUCAGUA AAAGCAAAGA	2801
AD-1566253	asusggu(Chd)AfgUfAf Afaagcaasgsa	3562	VPusUfscuuUfgCfUfuuu aCfuGfcauggsusc	3651	GCAUGGUCAGUAA AAGCAAAGAC	2802
AD-1566254	usgsugc(Ahd)GfuAfAf Afagcaagascsa	3563	VPusGfsuucUfuGfCfuuu uAfcUfgaccasusc	3652	CAUGGUCAGUAAA AGCAAAGACG	2803
AD-1566255	gsugsuca(Ghd)UfaAfAf Afgcaagacgsa	3564	VPusCfsgucUfuUfgfcuu uUfaCfugaccasusu	3653	AUGGUCAGUAAAA GCAAAGACGG	2804

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1566256	gsuscag(Uhd)AfaAfAfGfcaagacgsgsa	3565	VPusCfscguCfuUfUfgcuuUfuAfcugacscsa	3654	UGGUCAGUAAAAGCAAAGACGGG	2805
AD-1566257	uscsagu(Ahd)AfaAfGfCfaagacgsgsa	3566	VPusCfscgUfcUfUfugcuUfuUfacugascsc	3655	GGUCAGUAAAAGCAAAGACGGGA	2806
AD-1566258	csasgua(Ahd)AfaGfCfAfaagacgsgsa	3567	VPusUfscceGfuCfuUfuugcUfuUfuacugsasc	3656	GUCAGUAAAAGCAAAGACGGGAC	2807
AD-1566259	asgsuaa(Ahd)AfgCfAfAfagacgggascsa	3568	VPusGfsuccCfGfCfuuuGfuUfuucugsasc	3657	UCAGUAAAAGCAAAGACGGGACU	2808
AD-692906	asgsugu(Ghd)CfaAfAfUfagucuacasasa	3569	VPusUfsuguAfgAfCfuauuUfgCfacacugsc	3658	GCAGUGUGCAAAUAGUCUACAAA	1903
AD-1566575	gsusgca(Ahd)AfuAfGfUfcuacaaacsca	3570	VPusGfsguuUfgUfAfgacuAfuUfugacscasc	3659	GUGUGCAAAUAGUCUACAAAACCA	2835
AD-1566576	usgscaa(Ahd)UfaGfUfCfuacaaacsca	3571	VPusUfsgguUfuGfUfagacUfuUfugacscsa	3660	UGUGCAAAUAGUCUACAAAACCA	1904
AD-1566577	gsesaaa(Uhd)AfgUfCfUfacaaacsca	3572	VPusCfsuggUfuUfGfuagcUfuUfuugacscasc	3661	GUGCAAAUAGUCUACAAAACCA	315
AD-1566580	asasuag(Uhd)CfuAfCfAfaaccaguusgsa	3573	VPusCfsaacUfgGfUfuugcUfuUfuugacscasc	3662	CAAAUAGUCUACAAACCAGUUGA	321
AD-1566581	asusagu(Chd)UfaCfAfAfaccaguusgsa	3574	VPusUfscacCfuGfGfuuuGfuUfagacuuusgsa	3663	AAAUAGUCUACAAACCAGUUGAC	313
AD-1566582	usasguc(Uhd)AfcAfAfAfccaguugascsa	3575	VPusGfsucaAfcUfGfguuuGfuUfagacuuusgsa	3664	AAUAGUCUACAAACCAGUUGACC	324
AD-1566583	asgsucu(Ahd)CfaAfAfCfcaguugascsa	3576	VPusGfsgucAfaCfUfgguuUfgUfagacuasasa	3665	AUAGUCUACAAACCAGUUGACCU	319
AD-1566584	gsuscua(Chd)AfaAfCfCfaguugacsusa	3577	VPusUfsgguCfaAfCfugguUfuUfugacuasasa	3666	UAGUCUACAAACCAGUUGACCU	314
AD-1566586	csusaca(Ahd)AfcCfAfGfuugaccugsasa	3578	VPusUfscagGfuCfAfacuGfuUfugacuasasa	3667	GUCUACAAACCAGUUGACCU	334
AD-1566587	usascaaa(Ahd)CfcAfGfUfugaccugascsa	3579	VPusCfsucaGfgUfCfaacGfuUfugacuasasa	3668	UCUACAAACCAGUUGACCU	332
AD-1566588	ascsaaa(Chd)CfaGfUfUfugaccugascsa	3580	VPusGfscucAfgGfUfcaacUfgGfuugacuasasa	3669	CUACAAACCAGUUGACCU	353
AD-1566590	asasacc(Ahd)GfuUfGfAfccugagcasasa	3581	VPusUfsgucUfcAfGfgucAfaUfugacuasasa	3670	ACAAACCAGUUGACCU	337
AD-1566591	asasca(Chd)UfuGfAfCfcugagcaasgsa	3582	VPusCfsuugCfuCfAfgguuAfaCfugacuasasa	3671	CAAAACCAGUUGACCU	317
AD-1566634	asgsgea(Ahd)CfaUfCfCfaucuaaaacsca	3583	VPusGfsuuuAfuGfAfugguUfgUfugacuasasa	3672	UUAGGCAACAUCUACAUAUAAACC	340
AD-1566635	gsgscaa(Chd)AfuCfCfAfucuaaaacsca	3584	VPusGfsguuUfaUfGfaugGfuUfugacuasasa	3673	UAGGCAACAUCUACAUAUAAACC	330
AD-1566638	asascau(Chd)CfaUfCfAfuaaaccagsgsa	3585	VPusCfscugGfuUfUfauGfuUfugacuasasa	3674	GCAACAUCUACAUAUAAACCAGGA	1911
AD-1566639	ascsauc(Chd)AfuCfAfUfaaaccagsgsa	3586	VPusUfscuuGfgUfUfuauGfuUfugacuasasa	3675	CAACAUCUACAUAUAAACCAGGAG	2854
AD-1566641	asuscca(Uhd)CfaUfAfAfaccagagsgsa	3587	VPusCfscucCfuGfGfuuuUfgUfugacuasasa	3676	ACAUCUACAUAUAAACCAGGAGGU	2856
AD-1566642	uscscau(Chd)AfuAfAfAfccagagsgsa	3588	VPusUfscuuCfcUfGfguuuAfuUfugacuasasa	3677	CAUCAUCAUAAAACCAGGAGGU	2857
AD-1566643	csesauc(Ahd)UfaAfAfCfagagagsgsa	3589	VPusCfsaccUfcCfUfgguuUfaUfugacuasasa	3678	AUCAUCAUAAAACCAGGAGGU	2858
AD-1566679	asuscug(Ahd)GfaAfGfCfuugacuacsasa	3590	VPusUfsgaaGfuCfAfagcUfuUfugacuasasa	3679	AAUCUGAGAAGCUUGACUCAA	1912
AD-1566861	csasgea(Uhd)CfGfAfCfAfugguagacsusa	3591	VPusUfsgucUfaCfCfaugCfuUfugacuasasa	3680	GGCAGCAUCGACAUGGUAGACUC	1913
AD-1567153	usgsgea(Ghd)CfaAfCfAfaaggauusgsa	3592	VPusCfsaaaUfcCfUfuugcUfuUfugacuasasa	3681	AGUGGCAGCAACAAGGAUUUGA	1914

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1567154	gsgscag(Chd)AfaCfAfA faggauuugsasa	3593	VPusUfscAAAfUfCfuuu gUfuGfcuccsasc	3682	GUGGCAGCAACAA AGGAUUUGAA	1915
AD-1567157	asgscaa(Chd)AfaAfGf Gfauuugaaascsa	3594	VPusGfsuuuCfaAfAfucc uUfuGfuugcusc	3683	GCAGCAACAAAGG AUUUGAAACU	1916
AD-1567159	csasaca(Ahd)AfgGfAf Ufuugaacusus	3595	VPusAfsaguUfuCfAfaau cCfuUfuugucsu	3684	AGCAACAAAGGAU UUGAAACUUG	748
AD-1567160	asascaa(Ahd)GfgAfUf Ufugaacuugsusa	3596	VPusCfsaagUfuUfCfaaa uCfeUfuugucusc	3685	GCAACAAAGGAUU UGAAACUUGG	1918
AD-1567161	ascsaAa(Ghd)GfaUfUf Ufgaacuugsusa	3597	VPusCfscaaGfuUfUfcaa aUfcCfuugucusc	3686	CAACAAAGGAUUU GAAACUUGGU	1919
AD-1567164	asasgga(Uhd)UfuGfAf Afacuuggususa	3598	VPusAfsacCfaAfGfuuu cAfaAfuccuusc	3687	CAAAGGAUUUGAA ACUUGGUGUG	1922
AD-1567167	gsasuuu(Ghd)AfaAfCf Ufuggugususa	3599	VPusAfsacaCfaCfCfaagu UfuCfaaacsu	3688	AGGAUUUGAAACU UGGUGUGUUC	1923
AD-1567199	gsgscag(Ahd)CfGfAfUf Gfucaacuugsusa	3600	VPusCfsaagGfuUfGfaca uCfGfUfuccusc	3689	CAGGCAGACGAUG UCAACCUUGU	1924
AD-1567202	asgsacg(Ahd)UfgUfCf Afaccuugsusa	3601	VPusAfsacAfaGfGfuug aCfaUfGucusc	3690	GCAGACGAUGUCA ACCUUGUGUG	1925
AD-1567550	gsgscua(Ahd)CfcAfGf Ufucucuugsusa	3602	VPusAfscaaAfgAfGfaac uGfgUfuagccsu	3691	AGGGCUAACCAGU UCUCUUUGUA	1932
AD-1567554	asascaa(Ghd)UfuCfUf Cfuuguaaggsusa	3603	VPusCfsuuAfcAfAfaga gAfaCfugguusag	3692	CUAACCAAGUUC UUUGUAAGGA	1933
AD-1567784	uscsuca(Ghd)UfuCfCf Afcucaucasasa	3604	VPusUfsuggAfuGfAfgug gAfaCfugagasc	3693	ACUCUCAGUCCA CUCAUCCAAC	1948
AD-1567896	usasggu(Ghd)UfuUfCf Ufgccuugususa	3605	VPusCfsaacAfaGfGfcag aAfaCfaccuasc	3694	CCUAGGUGUUUCU GCCUUGUUGA	1949
AD-1567897	asgsug(Ghd)UfuCfUf Gfccuugususa	3606	VPusUfscAAAfUfGfgca gAfaAfaacusc	3695	CUAGGUGUUUCUG CCUUGUUGAC	1950
AD-1568105	asgsacg(Chd)UfgAfAf Cfauuacausasa	3607	VPusUfsaugUfaUfAfugu uCfaGfucusc	3696	GGAGCAGCUGAAC AUAUACAUAG	1954
AD-1568108	asgsucg(Ahd)AfcAfUf Afuaacuasusa	3608	VPusAfsuAfuGfUfaa uGfuUfagucusc	3697	GCAGCUGAACAU UACAUAGAUG	1955
AD-1568109	gsesuga(Ahd)CfaUfAf Ufacuagaususa	3609	VPusCfsaucUfaUfGfuau aUfgUfucusc	3698	CAGCUGAACAU ACAUGAUGU	1956
AD-1568139	gsasguu(Ghd)UfaGfUf Ufgauuugsusa	3610	VPusGfsacaAfaUfCfaac UfaCfaacusc	3699	UUGAGUUGUAGU GGAUUUGUCU	1961
AD-1568140	asgsuug(Uhd)AfgUfUf Gfgauuugsusa	3611	VPusAfsagAfaAfUfcca aCfuAfaacusc	3700	UGAGUUGUAGU GAUUUGUCUG	1962
AD-1568143	usgsuag(Uhd)UfgGfAf Ufuugucugususa	3612	VPusAfsacaGfaCfAfaau cCfaAfcuacasc	3701	GUUGUAGUUGGAU UUGUCUGUUU	1965
AD-1568144	gsusagu(Uhd)GfgAfUf Ufugucugususa	3613	VPusAfsaacAfgAfCfaaa uCfaAfaacusc	3702	UUGUAGUUGGAU UGUCUGUUUA	1966
AD-1568148	ususgga(Uhd)UfuGfUf Cfuguuuaagcsa	3614	VPusGfscauAfaAfCfaga cAfaAfuccaasc	3703	AGUUGGAUUUGUC UGUUUAUGCU	1968
AD-1568150	gsgsauu(Uhd)GfuCfUf Gfuuuuagcususa	3615	VPusAfsagAfuAfAfaca gAfaAfaacusc	3704	UUGGAUUUGUCUG UUUAUGCUUG	1969
AD-1568151	gsasuuu(Ghd)UfcUfGf Ufuuaugcususa	3616	VPusCfsaagCfaUfAfaaca GfaCfaaacsu	3705	UGGAUUUGUCUGU UUUAUGCUUG	1970
AD-1568152	asusuug(Uhd)CfuGfUf Ufuuaugcususa	3617	VPusCfscaaGfcAfUfaaac AfgAfaaacsu	3706	GGAUUUUGUCUGU UAUGCUUGGA	1971
AD-1568153	ususugu(Chd)UfgUfUf Ufaugcuugsusa	3618	VPusUfscAAAfGfAfuaa aCfaGfacaasc	3707	GAUUUGUCUGUUU AUGCUUGGAU	1972
AD-1568154	ususguc(Uhd)GfuUfUf Afugcuuggasusa	3619	VPusAfsuccAfaGfCfaaa aAfaAfaacasc	3708	AUUUGUCUGUUUA UGCUUGGAU	1973
AD-1568158	csusguu(Uhd)AfuGfCf Ufuggauucasc	3620	VPusGfsugaAfuCfCfaag cAfaAfaacasc	3709	GUCUGUUUAUGCU UGGAUUCACC	1976

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1568161	ususuu(Ghd)CfuUfGfGfauucaccasgsa	3621	VPusCfsuggUfgAfAfuccaAfgCfauaaascsa	3710	UGUUUAUGCUUGG AUUCACCAGA	1977
AD-1568172	asusuca(Chd)CfaGfAfGfugacuaggsasa	3622	VPusUfscuAfgUfCfacuUfgGfugaauscsc	3711	GAUUCACCAGAG UGACUAUGAU	1978
AD-1568174	uscsacc(Ahd)GfaGfUfGfauuagausasa	3623	VPusUfsaucAfuAfGfucaUfcUfggugasasu	3712	AUUCACCAGAGUG ACUAUGAUAG	1979
AD-1568175	csascca(Ghd)AfgUfGfAfcuagauasgsa	3624	VPusCfsuauCfaUfAfgucAfcUfcugugsasa	3713	UUCACCAGAGUGA CUAUGAUAGU	1980
AD-692908	ascscag(Ahd)GfuGfAfCfuaugauagsusa	3625	VPusAfsucaUfcAfUfaguAfcUfcugugsasa	3714	UCACCAGAGUGAC UAUGAUAGUG	1492
AD-1568176	cscsaga(Ghd)UfgAfCfUfaugauagsgsa	3626	VPusCfsacuAfuCfAfuagUcfaCfcucugsusg	3715	CACCAGAGUGACU AUGAUAGUGA	1982
AD-1569830	ascsaug(Ahd)AfaUfCfAfucuuagcsusa	3627	VPusAfsagcUfaAfGfaugAfuUfcauguscsc	3716	GGACAUGAAAUCA UCUUAGCUUA	2419
AD-1569832	asusgaa(Ahd)UfcAfUfCfuuaugcuasgsa	3628	VPusCfsuuaGfcUfAfagaUgfaUfuucausgsu	3717	ACAUGAAAUCAUC UUAGCUUAGC	2420
AD-1569834	gsasaau(Chd)AfuCfUfUfagcuuagcsusa	3629	VPusAfsgeuAfaGfCfuuaGfuGfauuucasu	3718	AUGAAAUCAUCUU AGCUUAGCUU	2421
AD-1569835	asasauc(Ahd)UfcUfUfAfcuuagcsusa	3630	VPusAfsagcUfaAfGfcuaAGfaUfgauuucsa	3719	UGAAAUCAUCUUA GCUUAGCUUU	2422
AD-1569862	gsusgaa(Uhd)GfuCfUfAfuauagugusasa	3631	VPusUfsacaCfuAfUfauaGafcAfuucacsasg	3720	CUGUGAAUGUCUA UAUAGUGUAU	755
AD-1569872	asusaua(Ghd)UfgUfAfUfuguguguususa	3632	VPusAfsaacAfcAfCfaauAfcCfuaauasasg	3721	CUAUUAUGUGUAU UGUGUGUUUU	2429
AD-1569890	csasaau(Ghd)AfuUfUfAfcacugacuggsa	3633	VPusCfsaguCfaGfUfguaAfuCfauuugsusu	3722	AACAAAUGAUUUA CACUGACUGU	2430
AD-1569892	asasuga(Uhd)UfuAfCfAfcugacugusasa	3634	VPusAfsacaGfuCfAfgugUafaAfucauusug	3723	CAAAUGAUUUACA CUGACUGUUG	2431

Example 2. *In Vivo* Evaluation in Transgenic Mice

This Example describes methods for the *in vivo* evaluation of MAPT RNAi agents in transgenic mice expressing human MAPT RNAs.

The ability of selected dsRNA agents designed and assayed in Example 1 are assessed for their ability to reduce the level of both sense- or antisense-containing foci in mice expressing human MAPT RNAs.

Briefly, duplexes of interest, identified from the above *in vitro* studies and shown in Tables 2-7 and 11-12, were evaluated *in vivo*. In particular, at pre-dose day 14 wild-type, 8 week old female mice (C57BL/6) were transduced by retroorbital administration of 2×10^{10} genome copies of AAV that expresses a portion of the human MAPT gene. In particular, mice were administered an AAV encoding a portion of human MAPT gene coding sequence (323-1648) and part of 3'UTR (4473-5811) of NM_016841.4, cloned in it.

Two weeks later and at day 0, the mice are administered subcutaneously a single dose of one of the dsRNA agents of interest at 3mg/Kg or PBS control. The administered duplexes are selected from AD-393752, AD-396420, AD-396425, AD-393239, AD-397167, AD-523561, AD-523565, AD-523562, and AD-535094. Two weeks' post-duplex dosing and at day 14, animals were sacrificed, liver

samples were collected and snap-frozen in liquid nitrogen. Tissue mRNA was extracted and analyzed by the RT-QPCR method for human MAPT expression.

Human MAPT mRNA levels were compared to housekeeping gene GAPDH. The values were then normalized to the average of PBS vehicle control group. The data were expressed as percent of baseline value, and presented as mean plus standard deviation. The results, listed in Table 29 and shown in Figure 1, demonstrate that the exemplary duplex agents tested effectively reduce the level of the human MAPT mRNA *in vivo*.

Table 29.

Group	Average	Std Dev
PBS	100	19
AD-393758	48	5
AD-396420	30	10
AD-396425	16	4
AD-393239	41	19
AD-397167	11	8
AD-523561	40	10
AD-523565	26	5
AD-523562	67	20
AD-535094	74	33

Example 3. *In Vivo* Evaluation of MAPT mRNA supression in Mice

This Example describes methods for the *in vivo* evaluation of MAPT RNAi agents in transgenic mice expressing human MAPT RNAs.

The ability of selected dsRNA agents designed and assayed in Tables 25-26 in Example 1 are assessed for their ability to reduce the level of both sense- or antisense-containing foci in mice expressing human MAPT RNAs.

Briefly, duplexes of interest, identified from the above *in vitro* studies and shown in Tables 25-26, were evaluated *in vivo*. In particular, the first study included 72 wild-type, 6-8 weeks old female mice (C57BL/6) that were transduced by retroorbital administration of 2×10^{10} genome copies of AAV that expresses a portion of the human MAPT gene at pre-dose day. The second study included 60 wild-type, 6-8 weeks old female mice (C57BL/6) that were transduced by retroorbital administration of 2×10^{10} genome copies of AAV that expresses a portion of the human MAPT gene at pre-dose day. In both the first and second studies, mice were administered an AAV encoding a portion of human MAPT gene coding sequence of NM_005910, cloned in it.

Two weeks later and at day 0, 48 mice in the first study divided into 16 groups of 3 animals per group, were administered subcutaneously a single dose of one of the dsRNA agents of interest at 3mg/Kg or PBS control. The administered duplexes are selected from AD-397167.1, AD-523565.1, AD-1397072.3, AD-1397073.3, AD-1397076.3, AD-1397077.3, AD-1397078.3, AD-1397252.2, AD-1397257.2, AD-1397258.2, AD-1397259.2, AD-1397263.2, AD-1397264.2, AD-1397309.2 and AD-

64958.114. Similarly, at day 0, 54 mice in the second study divided into 18 groups of 3 animals per group, were administered subcutaneously a single dose of one of the dsRNA agents of interest at 3mg/Kg or PBS control. The administered duplexes are selected from AD-397167.1, AD-393758.4, AD-1397080.3, AD-1397293.2, AD-1397294.2, AD-1397081.3, AD-1397083.3, AD-1397298.2, AD-1397299.2, AD-1397084.2, AD-1397085.2, AD-1397087.3, AD-1397306.2, AD-1397307.2, AD-1397308.2 and AD-1397088.2. Two weeks' post-duplex dosing and at day 14, animals in both the study were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen. Tissue mRNA was extracted and analyzed by the RT-QPCR method for human MAPT expression.

Human MAPT mRNA levels were compared to housekeeping gene GAPDH and normalized to the average of levels in the corresponding PBS vehicle control group. The data were expressed as percent of baseline value, and presented as mean plus standard deviation. The results, listed in Tables 29 and 30, respectively and shown in Figures 2 and 3, respectively. The results demonstrate that select exemplary duplex agents tested effectively reduce the level of the human MAPT mRNA *in vivo*.

15 **Table 29.**

Group	Average	Std Dev
PBS	100.0	19
AD-397167.1	13.0	9
AD-523565.1	3.9	3
AD-1397072.3	29.3	1
AD-1397073.3	82.7	36
AD-1397076.3	34.8	6
AD-1397077.3	50.0	15
AD-1397078.3	53.6	35
AD-1397252.2	17.0	7
AD-1397257.2	29.0	9
AD-1397258.2	23.8	9
AD-1397259.2	33.7	11
AD-1397263.2	59.6	6
AD-1397264.2	45.6	16
AD-1397309.2	65.9	37
AD-64958.114	21.2	6

Table 30.

Group	Average	Std Dev
PBS	105	11
AD-397167.1	18	5
AD-393758.4	38	5
AD-1397080.3	14	4
AD-1397293.2	32	7
AD-1397294.2	57	18
AD-1397081.3	28	12
AD-1397083.3	48	29
AD-1397298.2	50	18
AD-1397299.2	22	5

AD-1397084.2	41	19
AD-1397085.2	20	4
AD-1397087.3	58	24
AD-1397306.2	111	34
AD-1397307.2	40	26
AD-1397308.2	64	11
AD-1397088.2	21	1
AD-64958.114	49	20

EQUIVALENTS

- Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such
- 5 equivalents are intended to be encompassed by the scope of the following claims.

MAPT SEQUENCES

SEQ ID NO:1

>NM_016841.4 Homo sapiens microtubule associated protein tau (MAPT),
transcript variant 4, mRNA

5 GGACGGCCGAGCGGCAGGGCGCTCGCGCGCGCCCACTAGTGGCCGGAGGAGAAGGCTCCCGCGGAGGCCG
CGCTGCCCGCCCCCTCCCTGGGGAGGCTCGCGTTCCCGCTGCTCGCGCCTGCGCCGCCCGCCGGCCTCA
GGAACGCGCCCTCTTCGCCGGCGCGCCCTCGCAGTCACCGCCACCCACCAGCTCCGGCACCAACAGCA
GCGCCGCTGCCACCGCCACCTTCTGCCGCCGCCACCACAGCCACCTTCTCCTCCTCCGCTGTCTCTCC
CGTCTCGCCTCTGTGACTATCAGGTGAACCTTTGAACCAGGATGGCTGAGCCCCGCCAGGAGTTTCAAG

10 TGATGGAAGATCACGCTGGGACGTACGGGTGGGGGACAGGAAAGATCAGGGGGGCTACACCATGCACCA
AGACCAAGAGGGTGACACGGACGCTGGCCTGAAAGCTGAAGAAGCAGGCATTGGAGACACCCCCAGCCTG
GAAGACGAAGCTGCTGGTCACGTGACCCAAGCTCGCATGGTCAGTAAAAGCAAAGACGGGACTGGAAGCG
ATGACAAAAAAGCCAAGGGGGCTGATGGTAAAACGAAGATCGCCACACCGCGGGGAGCAGCCCCCTCCAGG
CCAGAAGGGCCAGGCCAACGCCACCAGGATTCCAGCAAAAACCCGCCCGCTCCAAAGACACCACCCAGC
15 TCTGGTGAACCTCCAAAATCAGGGGATCGCAGCGGCTACAGCAGCCCCGGCTCCCCAGGCACTCCCGGCA
GCCGCTCCCGCACCCCGTCCCTTCCAACCCACCCACCCGGGAGCCCAAGAAGGTGGCAGTGGTCCGTAC
TCCACCCCAAGTCGCGCTCTTCCGCCAAGAGCGCCTGCAGACAGCCCCCGTGCCCATGCCAGACCTGAAG
AATGTCAAGTCCAAGATCGGCTCCACTGAGAACCTGAAGCACCAGCCGGGAGGCGGGAAGGTGCAAATAG
TCTACAAACAGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACC
20 AGGAGGTGGCCAGGTGGAAGTAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGG
TCCCTGGACAATATCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCTGACCTTCC
CGGAGAACGCCAAAGCCAAGACAGACCACGGGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGA
CAGCTCTCCACGGCATCTCAGCAATGTCTCTCCACCGGCAGCATCGACATGGTAGACTCGCCCCAGCTC
GCCACGCTAGCTGACGAGGTGTCTGCCTCCCTGGCCAAGCAGGGTTTGTGATCAGGCCCCGCGGGGCGGTC
25 AATAATTGTGGAGAGGAGAGAATGAGAGAGTGTGAAAAAAGAAATAATGACCCGCCCCCGCCCTCT
GCCCCAGCTGCTCCTCGCAGTTCGGTTAATTGGTTAATCACTTAACCTGCTTTTGTCACTCGGCTTTGG
CTCGGGACTTCAAAATCAGTGATGGGAGTAAGAGCAAATTTTCATCTTTCCAAATTGATGGGTGGGCTAGT
AATAAAATATTTAAAAAACAATTCAAAAACATGGCCACATCCAACATTTCCCTCAGGCAATTCCTTTTG
ATTCTTTTCTTCCCTCCATGTAGAAGAGGGAGAAGGAGAGGCTCTGAAAGCTGCTTCTGGGGGATT
30 TCAAGGGACTGGGGGTGCCAACCCCTCTGGCCCTGTGTGGGGGTGTACAGAGGCAGTGGCAGCAACA
AAGGATTTGAAACTTGGTGTGTTCTGGAGCCACAGGCAGACGATGTCAACCTTGTGTGAGTGTGACGGG
GGTTGGGTGGGGCGGGAGGCCACGGGGGAGGCCAGGCAGGGGCTGGGCAGAGGGGAGAGGAAGCACAA
GAAGTGGGAGTGGGAGAGGAAGCCACGTGCTGGAGAGTAGACATCCCCCTCCTTGCCGCTGGGAGAGCCA
AGGCTATGCCACCTGCAGCGTCTGAGCGGCCGCTGTCTTGGTGGCCGGGGGTGGGGGCTGCTGTGG
35 GTCAGTGTGCCACCTCTGCAGGGCAGCCTGTGGGAGAAGGGACAGCGGTTAAAAAGAGAAGGCAAGCTG
GCAGGAGGTGGCACTTCGTGGATGACCTCCTTAGAAAAGACTGACCTTGATGTCTTGAGAGCGCTGGCC
TCTTCTCCTCCTCCTGCAGGGTAGGGGGCTGAGTTGAGGGGCTTCCCTCTGCTCCACAGAAACCTGTT
TTATTGAGTCTGAAGTTGGAACCTGCTGCCATGATTTTGGCCACTTTGCAGACCTGGGACTTTAGGGCT
AACCAGTTCTCTTTGTAAGGACTTGTGCCTCTTGGGAGACGTCCACCCGTTTCCAAGCCTGGGCCACTG
40 CATCTCTGGAGTGTGTGGGGGTCTGGGAGCTGAGTCCCGAGCCCCCTGTCTTCCCACGGCCACTGCAGT
CACCCCGTCTGCGCGCTGTGCTGTTCTGCTGCGGTGAGAGCCCAATCACTGCCTATACCCCTCATCACAC
GTCACAATGTCCCGAATTCACAGCCTCACCACCCCTTCTCAGTAATGACCCCTGGTTGGTTGCAGGAGGTA
CCTACTCCATACTGAGGGTGAAATTAAGGGAAGGCAAAGTCCAGGCACAAGAGTGGGACCCAGCCTCTC
ACTCTCAGTTCCACTCATCAACTGGGACCCTCACCACGAATCTCATGATCTGATTTCGGTTCCCTGTCTC
45 CTCCTCCCGTCACAGATGTGAGCCAGGGCACTGCTCAGCTGTGACCCTAGGTGTTTCTGCCTTGTGACA
TGGAGAGAGCCCTTTCCCTGAGAAGGCCTGGCCCTTCCCTGTGCTGAGCCACAGCAGCAGGCTGGGTG
TCTTGGTTGTCAAGTGGTGGCACCAGGATGGAAGGGCAAGGCACCCAGGGCAGGCCACAGTCCCGCTGTC
CCCCACTTGACCCCTAGCTTGTAGCTGCCAACCTCCCAGACAGCCAGCCCGCTGCTCAGCTCCACATGC
ATAGTATCAGCCCTCCACACCCGACAAAGGGGAACACACCCCTTGGAATGGTTCTTTTCCCCAGTCC
50 CAGCTGGAAGCCATGCTGTCTGTTCTGCTGGAGCAGCTGAACATATACATAGATGTTGCCCTGCCCTCCC
CATCTGCACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTACCAGAGTGACTATGATA
GTGAAAAGAAAAAAGGACGCATGTATCTTGAATGCTTGTAAAGAGGTTTCTAACCCTA
CCCTCACGAGGTGTCTCTACCCCCACACTGGGACTCGTGTGGCCTGTGTGGTGCCACCCCTGCTGGGGCC
TCCCAAGTTTTGAAAGGCTTTCCCTCAGCACCTGGGACCCAACAGAGACCAGCTTCTAGCAGCTAAGGAGG
55 CCGTTACAGCTGTGACGAAGGCCTGAAGCACAGGATTAGGACTGAAGCGATGATGTCCCTTCCCTACTTC
CCCTTGGGGCTCCCTGTGTGAGGGCACAGACTAGGTCTTGTGGCTGGTCTGGCTTGGGGCGCAGGATGG
TTCTCTCTGGTCATAGCCGAAGTCTCATGGCAGTCCCAAGGAGGCTTACAACCTCCTGCATCACAAGAA
AAAGGAAGCCACTGCCAGCTGGGGGATCTGCAGCTCCAGAAAGCTCCGTGAGCCTCAGCCACCCCTCAG
ACTGGGTTCTCTCCAAGCTCGCCCTCTGGAGGGGACGCGCAGCCTCCACCAAGGGCCCTGCGACCACA
60 GCAGGGATTGGGATGAATTGCCTGTCTGGATCTGCTCTAGAGGCCAAGCTGCCTGCCTGAGGAAGGAT

GACTTGACAAGTCAGGAGACACTGTTCCCAAAGCCTTGACCAGAGCACCTCAGCCCGCTGACCTTGACACA
AACTCCATCTGCTGCCATGAGAAAAGGGAAGCCGCTTTGCAAAACATTGCTGCCATAAGAACTCAGCA
GCCTCAGGCCCAATTCTGCCACTTCTGGTTTGGGTACAGTTAAAGGCAACCCTGAGGGACTTGGCAGTAG
AAATCCAGGGCCTCCCTGGGGCTGGCAGCTTCGTGTGCAGCTAGAGCTTTACCTGAAAGGAAGTCTCTG
5 GGCCCAAGAACTCTCCACCAAGAGCCTCCCTGCCGTTGCTGAGTCCCAGCAATTCTCCTAAGTTGAAGGG
ATCTGAGAAGGAGAAGGAAATGTGGGGTAGATTGGTGGTGGTTAGAGATATGCCCCCTCATTACTGCC
AACAGTTTCGGCTGCATTTCTTACGCACCTCGGTTCTCTCTCTGAAGTTCTGTGCCCTGCTCTTCAG
CACCATGGGCCTTCTTATACGGAAGGCTCTGGGATCTCCCCCTGTGGGGCAGGCTCTTGGGGCCAGCCT
AAGATCATGGTTTAGGGTGATCAGTGCTGGCAGATAAATTGAAAAGGCACGCTGGCTTGTGATCTTAAAT
10 GAGGACAAATCCCCCAGGGCTGGGCACTCCTCCCTCCCTCACTTCTCCACCTGCAGAGCCAGTGTCC
TTGGGTGGGCTAGATAGGATATACTGTATGCCGGCTCCTTCAAGCTGCTGACTCACTTTATCAATAGTTC
CATTTAAATTGACTTCAGTGGTGAGACTGTATCCTGTTTGTCTATTGCTTGTGTGCTATGGGGGGAGGGG
GGAGGAATGTGTAAGATAGTTAACATGGGCAAGGGAGATCTGGGGTGACAGCTTAAACTGCCTCGTA
ACCTTTTTCATGATTTCAACCACATTTGCTAGAGGGAGGGAGCAGCCACGGAGTTAGAGGCCCTTGGGGT
15 TTCTCTTTTCCACTGACAGGCTTTCCAGGCAGCTGGCTAGTTCACTTCCCTCCCCAGCCAGGTGCAGGCG
TAGGAATATGGACATCTGGTTGCTTTGGCCTGTGCCCTCTTTCAAGGGTCTTAAGCCCAATCATGCC
TCCCTAAGACCTTGGCATCCTTCCCTCTAAGCCGTGGGCACCTCTGTGCCACCTCTCACACTGGCTCCAG
ACACACAGCCTGTGCTTTTGGAGCTGAGATCACTCGCTTCACCTCCTCATCTTGTCTCCAAGTAAAG
CCACGAGTTCGGGGCAGGGCAGAGGTGATCACCTGCGTGTCCATCTACAGACCTGCAGCTTCATAAAA
20 CTTCTGATTTCTCTTCACTTTTGAAGGGTTACCCTGGGCACTGGCCTAGAGCCTCACCTCTAATAGA
CTTAGCCCCATGAGTTTGCCATGTTGAGCAGGACTATTTCTGGCACTTGCAAGTCCCATGATTTCTTCGG
TAATTCTGAGGGTGGGGGAGGGACATGAAATCATCTTAGCTTAGCTTTCTGTCTGTGAATGTCTATATA
GTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGTGAATTTGGAATAAAGTTA
TTACTCTGATTAAA

25 SEQ ID NO:2
>Reverse Complement of SEQ ID NO:1
TTTAATCAGAGTAATAACTTTATTTCCAAATTCACTTTACAGCAACAGTCAGTGTAATCATTTGTTAAACACA
CAATACACTATATAGACATTCACAGACAGAAAGCTAAGCTAAGATGATTTTCATGTCCCTCCCCCACCCTCAGAAT
30 TACCGAAGAAATCATGGGACTTGCAAGTGCCAGAAATAGTCTGCTCAACATGGCAAACCTCATGGGGCTAAG
TCTATTAGAGGTGAGGCTCTAGGGCAGTGCCAGGGTAACCTTTTCAAAGCTGAAGAGAAATCAGAAG
TTTTATGAAGCTGCAGGTCTGTAGATGGGACACGCAGGTGATCACCTCTGCCCTCGCCCCGACCTCGTGG
CTTTACTTGGAGAACAAGATGAGGAGGGTGAAGCGAGTGATCTCAGCTCCAAAAGCACAGGCTGTGTGT
CTGGAGCCAGTGTGAGAGGTGGCACAGAGGTGCCAACGGCTTAGAGGGAAGGATGCCAAGGTCTTAGGGA
35 GGCATGATTGTGGGCTTAGGACCCCTGAAAGAGGGCAGCAGGCCAAAGCAACCAGATGTCCATATTCCTA
CGCCTGCACCTGGCTGGGGAGGGAATGAACTAGCCAGCTGCCGAGGAAAGCCTGTGAGTGGAAAAGAGAA
ACCCCAAGGGCCTCTAATCCGTGGCTGCTCCCTCCCTCTAGCAAATGTGGTTGAAATCATGAAAAGGGT
TACGAGGCAGTTTAAAGTGCTGCACCCCAAGATCTCCCTTTGCCATGTTAACTATCTTACACATTCCTCC
CCCCCTCCCCCATAGCACACAAGCAATAGCAAACAGGATACAGTCTCACCCTGAAGTCAATTTAAATG
40 GAACTATTGATAAAGTGAGTCAGCAGCTTGAAGGAGCCGGCATACAGTATATCCTATCTAGCCACCCAA
GGACACTGGCTCTGCAGGTGGGAGAAGTGAGGGGAGGGGAGGAGTGCCAGCCCTGGGGGGATTGTCTC
ATTTAAGATCACAAGCCAGCGTGCCCTTTCAATTTATCTGCCAGCACTGATCACCTTAAACCATGATCTT
AGGCTGGCCCCCAAGCCTGCCCAACAAGGGGAGGATCCAGAGCCTTCCGTATAAGAAGGCCCATGTTG
45 CTGAAGAGCAGGGCACAAGAATTCAGGAAGAGGAACCGAGGTGCGTGAAGAAATGCAGCCGAAACTGTT
GGCAGTAATGAGGGGGCATATCTTAACCACCACCAATCTACCCACATTTCTTCTCTCTCAGAT
CCCTTCAACTTAGGAGAATTGCTGGGACTCAGCGAACCGCAGGGAGGCTCTTGGTGGAGAGTTCTGGGCC
CAGAGACTTCCTTTTCAAGTTAAAGCTCTAGCTGCACACGAAGCTGCCAGCCCCAGGGGAGGCCCTGGATTT
CTACTGCCAAGTCCCTCAGGGTTGCCCTTAACTGTACCCAAACCAGAAGTGGCAGAATTGGGCCTGAGGC
TGCTGAGTTTCTTTAGGCAGCAATGTTTGGCAAGGCGGCTTCCCTTTTCTCATGGCAGCAGATGGAGTT
50 TGTGCAAGGTGAGCGGGCTGAGGTGCTCTGGTCAAGGCTTTGGGAACAGTGCTCCTGACTTGTCAAGTC
ATCCTTCTCAGGCAGGCAGCTTGGGCTCTAGAGCAGATCCAGGACAGGCAATTCATCCCAATCCCTGC
TGTGGTTCGAGGGCCCTTGGTGGGAGGCTGCGCTGCCCTCCAGAGGGCGAGCTTGGAGAGGAACCCAGT
CTGAGGGGTGGCTGAGGCTCACGGAGCTTCTGGGAGCTGCAGATCCCCCAGCTGGCAGTGGCTTCCTTT
TTCTTGTGATGCAGGAGTTGTAAGCCTCCTTTGGGACTGCCATGAGACTTCGGGCTATGACCAGAGAGAA
55 CCATCCTCGCGCCGCAAGCCAGACCAGCCACAAGACCTAGTCTGTGCCCTGACACAGGAGCCCCAAGGG
GAAGTAGGGAAGGGGACATCATCGCTTCAGTCTTAATCCTGTGCTTCAGGCCCTTCGTACAGCTGAACGG
CCTCCTTAGCTGCTAGAAGCTGGTCTCTGTTGGGTCCAGGTGCTGAGGAAAGCCTTTCAAACCTTGGGA
GGCCCCAGCAGGGTGGCACCACACAGGCCACACAGTCCCAGTGTGGGGGTGAGAGACACCTCGTGAGGG
TGGGTTAGAAACCTCTTTACAAGCATTTCAAGATACATGCGTCTTTTTTTTTTTTTTTTTTCTTTTTCAC
60 TATCATAGTCACTCTGGTGAATCCAAGCATAAAGACAAATCCAACATACTCAACAGGGTGCAGATG
GGGAGGGCAGGGCAACATCTATGTATATGTTTCACTGCTCCAGCAGAACAGACAGCATGGCTTCCAGCTG

5 GGACTGGGGGAAAAGAACCATTTCCAAGGGGGTGTGTTCCCTTTGTGCGGGTGTGGAGGGCTGATACTAT
 GCATGTGGAGCTGAGCAGCGGGCTGGGCTGTCTGGGAGGTTGGCAGCTACAAGCTAGGGTGCAAGTGGGG
 GACAGCGGACTGTGGGCTGCCCTGGGTGCCTTGCCCTTCCATCCTGGTGCCACCCTGACAACCAAGA
 CACCCAGCCTGCTGCTGTGGGCTCAGCACAGGAAGGGGCCAGGCCTTCTCAGGGGAAAGGGCTCTCTCCA
 10 TGTCAACAAGGCAGAAACACCTAGGGTCACAGCTGAGCAGTGCCCTGGCTCACATCTGTGACGGGAGGAG
 GAGACAGGGAACCGAATCAGATCATGAGATTCTGGTGAGGGTCCCAGTTGGATGAGTGGAACCTGAGAGT
 GAGAGGCTGGGGTCCCACTCTTGTGCTGGACTTTGCCTTCCCTTAATTTACCCCTCAGTATGGAGTAGG
 TACCTCCTGCAACCAACCAGGGTCATTACTGAGAAGGGGTGGTGAGGCTGGGAATTCGGGACATTGTGAC
 GTGTGATGAGGGGTATAGGCAGTGATTGGGCTCTCACGGCAGACAACAGCACAGCGGCGCAGACGGGGTG
 15 ACTGCAGTGGCCGTGGGAAGGACAGGGGGCTCGGGACCTGCCTCCCAGACCCCAACACTCCAGAGATG
 CCAGTGGCCAGGCTTGAAACGGGTGGACGTCTCCCAAGAGGCACAAGTCTTACAAAGAGAAGTGGTT
 AGCCCTAAAGTCCCAGGTCTGCAAAGTGGCCAAAATCATGGCAGCAGTTCCAACCTTCAGAACTCAATAA
 AACAGGGTTTCTGTGGAGCAGAGGGAAGCCCCCTCAACTCAGGCCCCCTACCTGCAGGGAGGGAGGAAGA
 GGCCAGCGCTCTCAAGACATCAAGGTCAAGTCTTTTCTAAGGAGGTCATCCACGAAGTGCCACCCCTCCTGC
 20 CAGCTTGCCCTCTCTTTTTACCCGCTGTCCCTTCTCCACAGGCTGCCCTGCAGAGGGTGGCACACTGAC
 CCACAGCAGGCCCCACCCCGGCCACCAAGGACAGGCGGCCGCTCAGACGCTGCAGGTGGCATAGGCCT
 TGGCTCTCCAGCGCAAGGAGGGGGATGTCTACTCTCCAGCAGCTGGCTTCTCTCCACTCCCACTTC
 TTGTGCTTCTCTCCCTCTGCCAGCCCTGCCTCGGCCTCCCCCGTGGCTTCCCGCCCCACCCCAACC
 CCGCTCACACTCACACAAGGTTGACATCGTCTGCCTGTGGCTCCACGAACACCAAGTTTCAAATCTCTT
 25 TGTGCTGCCACTGCCTCTGTGACACCCCAACAGGGCCAGAGGTGGTTGGCACCCTCAGTCCCTTGA
 AATCCCCCAGAAGCAGCTTTCAGAGCCTCTCCTTCTCCCTCTTCTACATGGAGGGGAAGAAAAAGAAT
 CAAAAGGAATTGCCTGAGGAAATGTTGGATGTGGCCATGTTTTGAATGTTTTTTTTTAAATATTTTATT
 ACTAGCCACCCATCAATTTGGAAGATGAAATTTGCTCTTACTCCCATCACTGATTTTGAAGTCCCGAG
 CCAAAGCCGAGTGACAAAAGCAGGTTAAGTGATTAACCAATTAACCGAACTGCGAGGAGCAGCTGGGGG
 30 AGAGGGCGGGGGCCGGGTCATTATTCTTTTTTTTCCACACTCTCATTCTCTCTCTCCACAATTATT
 GACCGCCCCAGGGGCTGATCACAAACCTGCTTGGCCAGGGAGGCAGACACCTCGTCAGCTAGCGTGGC
 GAGCTGGGGCAGTCTACCATGTCTGATGCTGCCGTTGGAGGAGACATTGCTGAGATGCCGTGGAGACGTG
 TCCCCAGACACCACTGGCGACTTGTACACGATCTCCGCCCGTGGTCTGTCTTGGCTTTGGCGTTCTCGC
 GGAAGGTGAGCTTGTGGGTTTCAATCTTTTTATTTCTCCGCCAGGGACGTGGGTGATATGTGCCAGGGA
 35 CCAATCTTCGACTGGACTCTGTCTTGAAGTCAAGCTTCTCAGATTTTACTTCCACCTGGCCACCTCTCT
 GGTATTATGATGGATGTTGCCTAATGAGCCACACTGGAGGTCACCTTGTCTCAGGTCAACTGGTTGTAGA
 CTATTTGACACCTTCCCGCTCCCGGCTGGTGCTTCAGGTTCTCAGTGAGCCGATCTTGGACTTGACATT
 CTTAGGCTTGGCATGGGCACGGGGGCTGTCTGCAGGCGGCTCTTGGCGGAAGACGGCGACTTGGGTGGA
 GTACGGACCACTGCCACCTTCTTGGGCTCCCGGGTGGGTGGGGTTGGAAGGGACGGGGTGGCGGAGCGGC
 40 TGCCGGGAGTGCCCTGGGGAGCCGGGGCTGTCTGTAGCCGCTGCGATCCCCTGATTTTGGAGGTTTACCAGA
 GCTGGGTGGTGTCTTTGGAGCGGGCGGGGTTTTTGGCTGGAATCCTGGTGGCGTTGGCCTGGCCCTTCTGG
 CCTGGAGGGGCTGCTCCCGCGGTGTGGCGATCTTGTGTTTTTACCATCAGCCCCCTTGGCTTTTTGTCTAT
 CGCTTCCAGTCCCGTCTTTGCTTTTACTGACCATGCGAGCTTGGGTACAGTGACAGCAGCTTCGTCTTC
 CAGGCTGGGGGTGTCTCCAATGCCTGCTTCTTTCAGCTTTCAGGCCAGCGTCCGTGTACCCCTCTTGGTCT
 45 TGGTGCATGGTGTAGCCCCCTGATCTTTCCTGTCCCCCAACCGGTACGTCCAGCGTGATCTTCCATCA
 CTTTCAACTCCTGGCGGGGCTCAGCCATCCTGGTTCAAAGTTTCACTGATAGTCGACAGAGCGGAGGACG
 GGAGAGGACAGCGGAGGAGGAGAAGGTGGCTGTGGTGGCGGCGCAGAAGGTGGGCGGTGGCAGCGCGC
 TGCTGTTGGTACCGGAGCTGGTGGGTGGGTGACTGCGAGGGCGCGCGCCGGCGAAGAGGCGCGCTTCC
 TGAGGCCGCGGGCGCGCAGGCGGAGCAGCGGGAACGCGAGCCTCCCCAGGGGAGGGGCGGGCAGCG
 50 CGGCCTCCGCGGAGCCTTCTCTCCGGCCACTAGTGGGCGCGCGAGCGCCCTGCCGCTGGCGCGTCC

SEQ ID NO:3

>NM_005910.6 Homo sapiens microtubule associated protein tau (MAPT),
transcript variant 2, mRNA

50 GGACGGCCGAGCGGCAGGGCGCTCGCGCGGCCCACTAGTGGCCGGAGGAGAAGGCTCCCGCGGAGGCCG
 CGCTGCCCGCCCCCTCCCTGGGGAGGCTCGCGTTCCCGCTGCTCGCGCTGCGCCGCCCGCGGCCTCA
 GGAACGCGCCCTCTTCGCCGCGCGCGCCCTCGCAGTCACCGCCACCCACCAGCTCCGGCACCAACAGCA
 GCGCCGCTGCCACCGCCCACTTCTGCCGCGCCACCAACAGCCACCTTCTCTCTCTCCGCTGTCTCTCC
 55 CGTCTCTCGCTCTGTGACTATCAGGTGAATTTGAACAGGATGGCTGAGCCCCGCCAGGAGTTTGAAG
 TGATGGAAGATCACGCTGGGACGTACGGGTTGGGGGACAGGAAAGATCAGGGGGGCTACACCATGCACCA
 AGACCAAGAGGGTGACACGGACGCTGGCCTGAAAGAATCTCCCTGCAGACCCCCACTGAGGACGGATCT
 GAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGATGTGACAGCACCTTAG
 TGGATGAGGGAGCTCCCGCAAGCAGGCTGCCGCGCAGCCCCACACGGAGATCCCAGAAGGAACACAGC
 TGAAGAAGCAGGCATTGGAGACACCCCCAGCCTGGAAGACGAAGCTGCTGGTACGTGACCCAAGCTCGC
 60 ATGGTCAGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAGCCAAGGGGGCTGATGGTAAAACGA
 AGATCGCCACACCGCGGGAGCAGCCCTTCAGGCCAGAAGGGCCAGGCCAACGCCACAGGATTCCAGC

AAAAACCCCGCCCGCTCCAAAGACACCACCCAGCTCTGGTGAACCTCCAAAATCAGGGGATCGCAGCGGC
TACAGCAGCCCCGGCTCCCCAGGCACCTCCCGGCAGCCGCTCCCGCACCCCGTCCCTTCCAACCCACCCA
CCCGGGAGCCCAAGAAGGTGGCAGTGGTCCGTACTCCACCCAAGTCGCCGTCTTCCGCCAAGAGCCGCCT
GCAGACAGCCCCCGTGGCCATGCCAGACCTGAAGAATGTCAAGTCCAAGATCGGCTCCACTGAGAACCTG
5 AAGCACCAGCCGGGAGCGGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAACGTCCAGTCCA
AGTGTGGCTCAAAGGATAATATCAAAACAGTCCCGGGAGGCGGCAGTGTGCAAAATAGTCTACAAACCAGT
TGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACAGGAGGTGGCCAG
GTGGAAGTAAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCAAGATTGGGTCCCTGGACAATA
TCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCTGACCTTCCGCGAGAACGCCAA
10 AGCCAAGACAGACCACGGGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGACACGTCTCCACGG
CATCTCAGCAATGTCTCCTCCACCGGCAGCATCGACATGGTAGACTCGCCCCAGCTCGCCACGCTAGCTG
ACGAGGTGTCTGCCTCCCTGGCCAAGCAGGGTTTGTGATCAGGCCCCCTGGGGCGGTCAATAATTGTGGAG
AGGAGAGAATGAGAGAGTGTGGAAAAAAGAATAATGACCCGGCCCCCGCCCTCTGCCCCAGCTGCT
CCTCGCAGTTTCGGTTAATTGGTTAATCACTTAACCTGCTTTTGTCACTCGGCTTGGCTCGGGACTTCAA
15 AATCAGTGATGGGAGTAAGAGCAAATTTTCATCTTTCCAAATTGATGGGTGGGTAGTAATAAAAATATTTA
AAAAAAAACATTCAAAAACATGGCCACATCCAACATTTCTCAGGCAATTCCTTTTGATTCTTTTTCTT
CCCCCTCCATGTAGAAGAGGGGAGAAGGAGAGGCTCTGAAAGCTGCTTCTGGGGGATTTCAAGGGACTGGG
GGTGCCAACACCTCTGGCCCTGTTGTGGGGGTGTACAGAGGCAGTGGCAGCAACAAAGGATTTGAAAC
20 TTGGTGTGTTTCGTGGAGCCACAGGCAGACGATGTCAACCTTGTGTGAGTGTGACGGGGGTGGGGTGGG
CGGAGGCCACGGGGGAGGCCGAGGCAGGGCTGGGCAGAGGGGAGAGGAAGCACAAGAAGTGGGAGTGG
GAGAGGAAGCCACGTGCTGGAGAGTAGACATCCCCCTCCTTGGCGCTGGGAGAGCCAAGGCCTATGCCAC
CTGCAGCGTCTGAGCGGCCGCCTGTCTTGGTGGCCGGGGTGGGGGCCTGCTGTGGGTGAGTGTGCCAC
CCTCTGCAGGGCAGCCTGTGGGAGAGGGACAGCGGGTAAAAAGAGAAGGCAGCTGGCAGGAGGGTGGC
ACTTCGTGGATGACCTCCTTAGAAAAGACTGACCTTGATGTCTTGAGAGCGCTGGCCTCTTCTCCTCC
25 CTGCAGGGTAGGGGGCTGAGTTGAGGGGCTTCCCTCTGCTCCACAGAAACCCTGTTTTATTGAGTTCTC
AAGGTTGAAACTGCTGCCATGATTTTGGCCACTTTGCAGACCTGGGACTTTAGGGCTAACCAAGTCTCTT
TGTAAGGACTTGTGCCCTTGGGAGACGTCCACCCGTTTCCAAGCCTGGGCCACTGGCATCTCTGGAGTG
TGTGGGGTCTGGGAGGCAGGTCCCGAGCCCCCTGTCTTCCACGGCCACTGCAGTCACCCCGTCTGCG
CCGCTGTCTGTTGTCTGCCGTGAGAGCCCAATCACTGCCTATACCCCTCATCACACGTCACAATGTCCC
30 GAATTTCCAGCCTCACCACCCCTTCTCAGTAATGACCCTGGTTGGTTGCAGGAGGTACCTACTCCATACT
GAGGTGAAATTAAGGGAAGGCAAAAGTCCAGGCACAAGAGTGGGACCCAGCCTCTCACTCTGCTTCCA
CTCATCCAACCTGGGACCCCTCACCACGAATCTCATGATCTGATTTCGGTTCCCTGTCTCCTCCTCCCGTCAC
AGATGTGAGCCAGGGCACTGCTCAGCTGTGACCCTAGGTGTTTCTGCCTTGTGACATGGAGAGAGCCCT
TTCCCTGAGAAGGCCGTGGCCCCCTTCTGTGCTGAGCCACAGCAGCAGGCTGGGTGTCTTGGTTGTGAG
35 TGGTGGCACCAGGATGGAAGGGCAAGGCACCCAGGGCAGGCCACAGTCCCGCTGTCCCCCACTTGCACC
CTAGCTTTGTAGCTGCCAACCTCCCAGACAGCCAGCCCGCTGCTCAGCTCCACATGCATAGTATCAGCCC
TAGACACCCGACAAAGGGGAACACACCCCTTGGAAATGGTTCTTTTCCCCAGTCCGAGCTGGAAGCCA
TGCTGTCTGTTCTGCTGGAGCAGCTGAACATATACATAGATGTTGCCCTGCCCTCCCCATCTGCACCCTG
TTGAGTTGTAGTTGGATTGTCTGTTTATGCTTGGATTACCCAGAGTGACTATGATAGTAAAAAGAAAAA
40 AAAAAAAAAAAGGACGCATGTATCTTGAAATGCTTGTAAGAGGTTTCTAACCCACCCCTCACGAGGTG
TCTCTACCCCCACACTGGGACTCGTGTGGCCTGTGTGGTGCCACCCTGCTGGGGCCTCCCAAGTTTGA
AAGGCTTTCTCAGCACCTGGGACCCAACAGAGACCAGCTTCTAGCAGCTAAGGAGGCCGTTTCAGCTGTG
ACGAAGGCTTAAGCACAGGATTAGGACTGAAGCGATGATGTCCCTTCCCTACTTCCCTTGGGGCTCC
CTGTGTGAGGGCACAGACTAGGTCTTGTGGCTGGTCTGGCTTGGCGCGCAGGATGGTTCTCTGTGTC
45 TAGCCCGAAGTCTCATGGCAGTCCCAAAGGAGGCTTACAACCTCTGCATCACAAGAAAAAGGAAGCCACT
GCCAGCTGGGGGATCTGCAGCTCCCAAGCTCCGTGAGCCTCAGCCACCCCTCAGACTGGGTTCCTCT
CCAAGCTCGCCCTCTGGAGGGGCAGCGCAGCCTCCACCAAGGGCCCTGCGACCACAGCAGGGATTGGGA
TGAATTGCCTGTCTTGATCTGCTCTAGAGGCCAAGCTGCCCTGCTGAGGAAGGATGACTTGACAAGTC
AGGAGACACTGTTCCCAAAGCCTTGACCAGAGCAGCTCAGCCCGCTGACCTTGACAAAACTCCATCTGCT
50 GCCATGAGAAAAGGGAAGCCGCCTTTGCAAAACATTGCTGCCTAAAGAACTCAGCAGCCTCAGGCCCAA
TTCTGCCACTTCTGGTTTGGGTACAGTTAAAGGCAACCCTGAGGGACTTGGCAGTAGAAATCCAGGGCCT
CCCCTGGGGCTGGCAGCTTCTGTGTGAGCTAGAGCTTTACCTGAAAGGAAGTCTCTGGGGCCAGAACTCT
CCACCAAGAGCCTCCCTGCCGTTTCGTGAGTCCCAGCAATTCCTTAAGTTGAAGGGATCTGAGAAGGAG
AAGGAAATGTGGGTAGATTGGTGGTGGTTAGAGATATGCCCCCTCATTACTGCCAACAGTTTCGGCT
55 GCATTTCTTACGCACCTCGGTTCTCTTCTGAGTTCCTTGTGGCCTGCTCTTACGACCATGGGCCTT
CTTATACGGAAGGCTCTGGGATCTCCCCCTTGTGGGGCAGGCTCTTGGGGCCAGCCTAAGATCATGGTTT
AGGGTGATCAGTGTGCGAGATAAATTGAAAAGGCACGCTGGCTGTGATCTTAAATGAGGACAATCCCC
CCAGGGCTGGGCACTCTCCCTCCCTCACTTCTCCACCTGCAGAGCCAGTGTCTTGGGTGGGCTAG
ATAGGATATACTGTATGCCGGCTCCTTCAAGCTGCTGACTCACTTTATCAATAGTTCCATTTAAATTGAC
60 TTCAGTGGTGAGACTGTATCCTGTTTGCTATTGCTTGTGTGCTATGGGGGAGGGGGGAGGAATGTGTA
AGATAGTTAACATGGGCAAGGGAGATCTTGGGGTGCAGCACTTAAACTGCCTCGTAACCCCTTTTCATGA

TTTCAACCACATTTGCTAGAGGGAGGGAGCAGCCACGGAGTTAGAGGCCCTTGGGGTTTCTCTTTTCCAC
TGACAGGCTTTCCAGGCAGCTGGCTAGTTCATTCCCTCCCCAGCCAGGTGCAGGCGTAGGAATATGGAC
ATCTGGTTGCTTTGGCTGCTGCCCTCTTTAGGGGTCTAAGCCCACAATCATGCCTCCCTAAGACCTT
GGCATCCTTCCCTCTAAGCCGTTGGCACCTCTGTGCCACCTCTCACACTGGCTCCAGACACACAGCCTGT
5 GCTTTTGGAGCTGAGATCACTCGCTTCACCCTCCTCATCTTTGTCTCCAAGTAAAGCCACAGGTCGGG
GCGAGGGCAGAGGTGATCACCTGCGTGTCCCATCTACAGACCTGCAGCTTCATAAAACTTCTGATTTCTC
TTCAGCTTTGAAAAGGGTTACCCTGGGCACTGGCTAGAGCCTCACCTCCTAATAGACTTAGCCCCATGA
GTTTGCCATGTTGAGCAGGACTATTTCTGGCACTTGCAAGTCCCATGATTTCTCGGTAATTCTGAGGGT
GGGGGGAGGGACATGAAATCATCTTAGCTTAGCTTTCTGTCTGTGAATGTCTATATAGTGTATTGTGTGT
10 TTTAACAAATGATTTACTGACTGTTGCTGTAAAAGTGAATTTGAAATAAAGTTATTACTCTGATTAA
A

SEQ ID NO:4

>Reverse Complement of SEQ ID NO:3

15 TTTAATCAGAGTAATAACTTTATTTCCAAATTCACCTTTTACAGCACAGTCAGTGTAATCATTTGTAAAA
ACACACAATACACTATATAGACATTACAGACAGAAAGCTAAGCTAAGATGATTTTCATGTCCCTCCCCC
ACCCTCAGAATTACCGAAGAAATCATGGGACTTGCAAGTGCCAGAAATAGTCTGCTCAACATGGCAAAC
TCATGGGGCTAAGTCTATTAGGAGGTGAGGCTCTAGGCCAGTGCCAGGGTAACCCCTTTTCAAAGCTGAA
GAGAAATCAGAAGTTTTATGAAGCTGCAGGTCTGTAGATGGGACACGCAGGTGATCACCTCTGCCCTCGC
20 CCCGACCTCGTGGCTTTTACTTGGAGAACAAAGATGAGGAGGGTGAAGCGAGTGATCTCAGCTCCAAAAGC
ACAGGCTGTGTCTGGAGCCAGTGTGAGAGGTGGCACAGAGGTGCCAACGGCTTAGAGGGAAGGATGCC
AAGGTCTTAGGGAGGCATGATTGTGGCTTAGGACCCCTGAAAGAGGGCAGCAGGCCAAAGCAACCAGAT
GTCCATATTCCTACGCCTGCACCTGGCTGGGGAGGGAATGAAGTAGCCAGCTGCCTGGGAAAGCCTGTCA
GTGGAAAAGAGAAACCCCAAGGGCTCTAACTCCGTGGCTGCTCCCTCCCTCTAGCAAATGTGGTTGAAA
25 TCATGAAAAGGGTTACGAGGCAGTTTAAGTGCTGCACCCCAAGATCTCCCTTTGCCCATGTTAACTATCT
TACACATTCCTCCCCCTCCCCCATAGCACAAAGCAATAGCAAAACAGGATACAGTCTCACCCTGAA
GTCAATTTAAATGGAATATTGATAAAGTGAGTCAGCAGCTTGAAGGAGCCGGCATACAGTATATCCTAT
CTAGCCCACCCAAGGACACTGGCTCTGCAGGTGGGAGAAGTGAGGGGAGGGGAGGAGTGCCAGCCCTGG
GGGGATTGCTCTCATTTAAGATCACAAAGCCAGCGTGCCTTTTCAATTTATCTGCCAGCACTGATCACCT
30 AAACCATGATCTTAGGCTGGCCCCAAGAGCCTGCCCCACAAGGGGGAGATCCCAGAGCCTTCCGTATAAG
AAGGCCCATGGTGCTGAAGAGCAGGGCACAAAGAACTTCAGGAAGAGGAACCGAGGTGCGTGAAGAAATGC
AGCCGAAACTGTTGGCAGTAATGAGGGGGGCATATCTCTAACCACCACCAAATCTACCCACATTTCTCT
CTCCTTCTCAGATCCCTTCAACTTAGGAGAATTGCTGGGACTCAGCGAACGGCAGGGAGGCTCTTGGTGG
AGAGTTCTGGGCCCAGAGACTTCCCTTCAGGTAAAGCTCTAGCTGCACACGAGCTGCCAGCCCCAGGGG
35 AGGCCCTGGATTTCTACTGCCAAGTCCCTCAGGGTTGCCTTTAACTGTACCCAAACAGAAAGTGGCAGAA
TTGGGCTGAGGCTGCTGAGTTTCTTTAGGCAGCAATGTTTTGCAAAGGGCGCTTCCCTTTTCTCATGGC
AGCAGATGGAGTTTGTGCAAGGTCAGCGGGCTGAGGTGCTCTGGTCAAGGCTTTGGGAACAGTGTCTCCT
GACTTGCAAGTCATCCTTCTCAGGCAGGCAGCTTGGGCTCTAGAGCAGATCCAGGACAGGCAATTCA
TCCCAATCCCTGCTGTGGTTCGAGGGCCCTTGGTGGGAGGCTGCGCTGCCCTCCAGAGGGCGAGCTTGG
40 AGAGGAACCCAGTCTGAGGGGTGGCTGAGGCTCAGCGAGCTTCTGGGAGCTGCAGATCCCCCAGCTGGC
AGTGGCTTCTCTTTTCTGTGATGCAGGAGTTGTAAGCCTCCTTTGGGACTGCCATGAGACTTCGGGCTA
TGACCAGAGAGAACCATCCTCGCGCCGCAAGCCAGACCAGCCACAAGACCTAGTCTGTGCCCTGACACAG
GGAGCCCATGGGAAAGTAGGGAAGGGGACATCCTGCTTCAGTCTAATCCTGTGCTTCAGGCTTCGT
CACAGCTGAACGGCTCCTTAGCTGCTAGAAGCTGGTCTCTGTTGGGTCCCAGGTGCTGAGGAAAGCCTT
45 TCAAAACTTGGGAGGGCCCCAGCAGGTTGGCACCACACAGGCCACACGAGTCCCAGTGTGGGGGTGAGAGA
CACCTCGTGAGGGTGGGTTAGAAACCTCTTTACAGCATTTCAAGATACATGCGTCCTTTTTTTTTTTTT
TTTTTCTTTTCACTATCATAGTCACTCTGGTGAATCCAAGCATAAACAGACAAATCCAACACAACCTCAA
CAGGGTGCAGATGGGGAGGGCAGGGCAACATCTATGTATATGTTTCAGCTGCTCCAGCAGAACAGACAGCA
TGGCTTCCAGCTGGGACTGGGGGAAAAGAACATTTCCAAGGGGGTGTGTTCCCTTTTGTGCGGGTGTGGA
50 GGGCTGATACTATGCATGTGGAGCTGAGCAGCGGGCTGGGCTGTCTGGGAGGTTGGCAGCTACAAGCTAG
GGTGAAGTGGGGGACAGCGGGACTGTGGGCTGCCCTGGGTGCCTTGGCTTCCATCCTGGTGGCACC
CTGACAACCAAGACACCCAGCCTGCTGCTGTGGCTCAGCACAGGAAGGGGCCAGGCCTTCTCAGGGGAA
AGGGCTCTCTCCATGTCAACAAGGCAGAAACACCTAGGGTCACAGCTGAGCAGTGCCCTGGCTCACATCT
GTGACGGGAGGAGAGACAGGGAACCGAATCAGATCATGAGATTCGTGGTGAGGGTCCAGTTGGATGAG
55 TGGAACTGAGAGTGAGAGGCTGGGGTCCCACTCTGTGCCTGGACTTTGCCTTCCCTTAATTTCAACCTC
AGTATGGAGTAGGTACCTCCTGCAACCAACCAGGGTCATTACTGAGAAGGGGTGGTGGGCTGGGAATTC
GGGACATTGTGACGTGTGATGAGGGGTATAGGCAGTGATTGGGCTCTCACGGCAGACAACAGCACAGCGG
CGCAGACGGGGTGACTGCAGTGGCCGTGGGAAGGACAGGGGGCTCGGGACCTGCCCTCCAGACCCCCACA
CACTCCAGAGATGCCAGTGGCCCAGGCTTGGAAACGGGTGGACGTCTCCCAAGAGGCACAAGTCTTACA
60 AAGAGAACTGGTTAGCCCTAAAGTCCCAGGTCTGCAAAGTGGCCAAAATCATGGCAGCAGTTCCAACCTT
CAGAACTCAATAAAACAGGGTTTCTGTGGAGCAGAGGGAAGCCCTCAACTCAGGCCCCCTACCCTGCAG

5 GGAGGGAGGAAGAGGCCAGCGCTCTCAAGACATCAAGGTCAGTCTTTTCTAAGGAGGTCATCCACGAAGT
 GCCACCCCTCCTGCCAGCTTGCCCTTCTTTTTACCGCTGTCCCTTCTCCACAGGCTGCCCTGCAGAGG
 GTGGCACACTGACCCACAGCAGGCCCCACCCCGGCCACCAAGGACAGGCGGCCGCTCAGACGCTGCAG
 GTGGCATAGGCCCTTGCTCTCCCAGCGGCAAGGAGGGGATGTCTACTCTCCAGCACGTGGCTTCTCTC
 10 CCACTCCCACTTCTTGCTTCCCTCTCCCTCTGCCAGCCCTGCCTCGGCCTCCCCCGTGGCCTCCCG
 CCCCACCCCAACCCCGTCACACTCACACAAGGTTGACATCGTCTGCCTGTGGCTCCACGAACACACCAA
 GTTTCAAATCCTTTGTGTGCTGCCACTGCCTCTGTGACACCCCAACAACAGGGCCAGAGGTGGTTGGCACC
 CCCAGTCCCTTGAAATCCCCCAGAAGCAGCTTTTACAGAGCCTCTCCTTCTCCCTCTTCTACATGGAGGGGG
 AAGAAAAAAGAATCAAAAGGAATTGCCTGAGGAAATGTTGGATGTGGCCATGTTTTTGAATGTTTTTTTT
 15 TAAATATTTTATTACTAGCCACCCATCAATTTGAAAGATGAAATTTGCTCTTACTCCCATCACTGATT
 TTGAAGTCCCAGCCAAAGCCGAGTGACAAAAGCAGGTTAAGTGATTAACCAATTAACCGAAGTGCAGAG
 AGCAGCTGGGGGAGAGGGCGGGGGCGGGTGCATTATTCTTTTTTTTCCACACTCTCTCATTCTCTCCT
 CTCCACAATTATTGACCGCCCCAGGGGCTGATCACAACCCCTGCTTGGCCAGGGAGGACAGACCTCGT
 CAGCTAGCGTGGCGAGCTGGGGCGAGTCTACCATGTGATGCTGCCGGTGGAGGAGACATTGCTGAGATG
 20 CCGTGGAGACGTGTCCCAGACACCACTGGCGACTTGTACACGATCTCCGCCCCGTGGTCTGTCTTGGCT
 TTGGCGTTCTCGCGGAAGGTCAGCTTGTGGGTTTCAATCTTTTTATTTCCTCCGCCAGGGACGTGGGTGA
 TATTGTCCAGGGACCAATCTTCGACTGGACTCTGTCTTGAAGTCAAGCTTCTCAGATTTTACTTCCAC
 CTGGCCACCTCCTGGTTATGATGGATGTTGCCTAATGAGCCACACTTGGAGGTCACCTTGCTCAGGTCA
 ACTGGTTTGTAGACTATTGACACTGCCGCTTCCGGGACGTGTTTGATATTATCCTTTGAGCCACACT
 25 TGGACTGGACGTTGCTTAAGATCCAGCTTCTTATTAATTATCTGCACCTTCCCGCCTCCCGGCTGGTGCTT
 CAGGTTCTCAGTGGAGCCGATCTTGGACTTGACATTCTTCAGGTCTGGCATGGGCACGGGGGCTGTCTGC
 AGGCGGCTCTTGGCGGAAGACGGCGACTTGGGTGAGTACGGACCACTGCCACCTTCTTGGGCTCCCGGG
 TGGGTGGGTTGGAAGGACGGGGTGGGGAGCGGCTGCCGGGAGTGCCTGGGGAGCCGGGGCTGCTGTA
 GCGCTGCGATCCCCGATTTTGGAGGTTACACAGAGCTGGGTGGTGTCTTTGGAGCGGGCGGGGTTTTT
 30 GCTGGAATCCTGGTGGGCTTGGCCTGGCCCTTCTGGCCTGGAGGGGCTGCTCCCCGCGGTGAGCGATCT
 TCGTTTTTACCATCAGCCCCCTTGGCTTTTTTGTCTATCGCTTCCAGTCCCGTCTTTGCTTTTACTGACCAT
 GCGAGCTTGGGTACGTGACCAGCAGCTTCTGCTTCCAGGCTGGGGGTGTCTCCAATGCCTGCTTCTTCA
 GCTGTGGTTCTTCTGGGATCTCCGTGTGGGGCTGCGCGGCAGCCTGCTTGGCGGGAGCTCCCTCATCCA
 CTAAGGGTGCTGTACATCTTCCGCTGTTGGAGTGCTCTTAGCATCAGAGGTTTTCAGAGCCCCGTTCTCTC
 35 AGATCCGTCCTCAGTGGGGGTCTGCAGGGGAGATTCTTTCAGGCCAGCGTCCGTGTACCCCTCTTGGTCT
 TGGTGCATGGTGTAGCCCCCTGATCTTCTGTGTCCTTCCCAACCCGTACGTCCAGCGTGTCTTCCATCA
 CTTCGAACTCCTGGCGGGGCTCAGCCATCCTGGTTCAAAGTTACCTGATAGTCGACAGAGGCGAGGACG
 GGAGAGGACAGCGGAGGAGGAGAAGGTGGCTGTGGTGGCGGCGGAGAGGTGGGCGGTGGCAGCGGCGC
 TGCTGTTGGTGCCGGAGCTGGTGGGTGGCGGTGACTGCGAGGGCGCGCGCCGCGGAAGAGGGCGCGTTCC
 40 TGAGGCCGGCGGGCGGCGCAGGCGGAGCAGCGGGAACGCGAGCCTCCCCAGGGGAGGGGGCGGGCAGCG
 CGGCCTCCGCGGGAGCCTTCTCCTCCGGCCACTAGTGGGCGCGCGGAGCGCCCTGCGCTCGGCCGTCC

SEQ ID NO:5

40 >NM_001038609.2 Mus musculus microtubule-associated protein tau (Mapt),
 transcript variant 1, mRNA
 CCGCCGGCTCCAGAACCGCGCTTTCTCGGCCGCGCGCTCTCAGTCTCCGCCACCCACCAGCTCCAGCA
 CCAGCAGCAGCGCCCGCCACCGCCACCTTCTGCGCGCGCGCCACAACCACCTTCTCCTCCGCTGTC
 CTCTTCTGCTCGCTTCTGTGATATCAGGCTTTGAACCAAGTATGGCTGACCTCGCCAGGATTG
 45 ACACAATGGAAGACCATGCTGGAGATTACACTCTGCTCCAAGACCAAGAAGGAGACATGGACCATGGCTT
 AAAAGAGTCTCCCCACAGCCCCCGCCGATGATGGAGCGGAGGAACCAGGGTCGGAGACCTCCGATGCT
 AAGAGCACTCCAAGTGTGAAGACGTGACTGCGCCCTAGTGGATGAGAGAGCTCCCGACAAGCAGGCCG
 CTGCCCAGCCCCACACGGAGATCCCAAGAAGGAATTACAGCCGAAGAAGCAGGCATCGGAGACACCCGAA
 CCAGGAGGACCAAGCCGCTGGGCATGTGACTCAAGCTCGTGTGGCCAGCAAGACAGGACAGGAAATGAC
 50 GAGAAGAAAGCCAAAGGCGCTGATGGCAAAACCGGGCGAAGATCGCCACACCTCGGGGAGCAGCCTCTC
 CGGCCCAAGAAGGACGTCCAACGCCACCAGGATCCCGGCCAAGACCAGCCAGCCCTAAGACTCCTCC
 AGGGTCAGGTGAACCACCAAAATCCGAGAACGAAGCGGCTACAGCAGCCCCGGCTCTCCCGGAACGCCT
 GGCAGTCGCTCGCGCACCCATCCCTACCAACACCGCCACCCGGGAGCCCAAGAAGGTGGCAGTGGTCC
 GCACTCCCCCTAAGTCACCATCAGCTAGTAAGAGCCGCTGCAGACTGCCCCGTGTCCTATGCCAGACCT
 55 AAAGAATGTCAGGTGGAAGATTGGCTCTACTGAGAACCTGAAGCACCAGCCAGGAGGTGGCAAGGTGAC
 ATAATTAATAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCGAAGGATAATATCAAAACACG
 TCCCGGTGGAGGACGTGTGCAAATAGTCTACAAGCCGCTGGACCTGAGCAAAGTGACCTCCAAGTGTGG
 CTCGTTAGGGAACATCCATCACAAGCCAGGAGGTGGCCAGGTGGAAGTAAATCAGAGAAGCTGGACTTC
 AAGGACAGAGTCCAGTGAAGATTGGCTCCTTGATAATATACCCACGTCCCTGGAGGAGGGAATAAGA
 60 AGATTGAAACCCACAAGCTGACCTTCAGGGAGAATGCCAAAGCCAAGACAGACCATGGAGCAGAAATTTGT
 GTATAAGTCAACCGTGGTGTCTGGGGACACATCTCCACGGCACCTCAGCAATGTGTCTTCCACGGGCAGC
 ATCGACATGGTGGACTCACACAGCTTGCCACACTAGCCGATGAAGTGTCTGCTTCTTGGCCAAGCAGG

5 GTTTGTGATCAGGCTCCCAGGGCAGTCAATAATCATGGAGAGAAGAGAGAGTGAAGTGTGGAAAAA
AAAAAAGAAATGATCTGGCCCCCTTGCCCTCTGCCCTCCCCGCTGCTCCTCATAGACAGGCTGACCTGC
TTGTCACCTAACCTGCTTTTGTGGCTCGGATTTGGCTCGGGACTTCAAAATCAGTGATGGGAAAAGTACA
TTTCATCTTTCCAAATGATTTGTGGGCTAAAAATAAACATATTTAAGGGAAAAAATCATGTAAAAA
10 CATGGCCAAAAAATTTCTTGGGCAATTGCTAATTGATTTCCCCCCCCCTGACCCCGCCCTCCCTCTCTGA
GTATTAGAGGGTGAAGAAGGCTCTGGAGGCTGCTTCTGGGGAGTGGCTGAGGGACTAGGGCAGCTAATTG
CCCATAGCCCCATCTAGGGGCTTCAGGGACAGTGGCAGCAATGAGAGATTGAGACTTGGTGTGTTTCGT
GGGGCCGTAGGCAGGTGCTGTTAACTTGTGTGGGTGTGAGTGGGGACTGAAACAGCGACAGCGAAGGCTG
AGAGATGGATGGGTGGACTGAGTTAGAGGACAGAGGTGAGGAAGGCAGGTTGGGAGAGGGGACACTGGCT
15 CCTTGCCAAGTAGCTTGGGGAGGACAGGGTGTGTCAGCTGCCCTGCAGCAGTCTAGCTAGCTCAGATGCC
TGCTTGATAAAGCACTGTGGGGGTAACTGAGGTGTGTGTGCCCTTCTGCAGGGCAGCCTGTGGGAGAAG
GGGTATTGGGCAGAAGGAAGGTAAGCCAGCAGGTGGTACCTTGTAGATTGGTCTCTTGAAGGCTGCTCT
TGACATCCCAGGGCACTGGCTTCTTCCCTCCCTCCCGCAAGGTGGGAGGTCTGAGCGAGGTGTTTCCCT
20 TCGCTCCACAGGAAAAGCTGCTTTACTGAGTTCTCAAGTTTGAACCTACAGCCATGATTTGGCCACCAT
TACAGACCTGGGACTTTAGGGCTAACAGATCTTTGTAAGGACTTGTGCCTCTTGGGGGACCTCTGCCTG
TTCTCATGCTTGGCCCTCTGGCACTTCTGTAGTGGGAGGGATGGGGGTGGTATTCTGGGATGTGGGTCC
CAGGCCTCCCATCCCTCACACAGCCACTGTATCCCTCTCTCTGTCTATCATGCCACGCTGTGCCACGA
GAGCTAGTCACTGCCGTCCGTACATCACGTCTCACTGTCTGAGTGCCATGCCCTCTCCAGCCCCCATCC
25 CTGGCCCCCTGGGTAGATATGGGCAATATCTGCTCTACACTAGGGGTGGAGTCCAGGGAAGGCAAGATT
TGGGCCCTCAGTCTCTAGTCTACGTTCACGAATCCAACCAAGTGTGCCTCCACAAAGGAACCTTACGACC
TTGTTTGGTTCACTCCATTACTTCCATCTCTGGATGGGAACGTGTGTGTGCCTGCCTGGGGATGACCTTG
GACCTCTGCCTTTTCTTTTATCTAAGTGGATGCCTCTAGGCCTGACTCCTTGTGTTGAGCTGGAGGCAG
CCAAGTCAAGTGCCAAATGTCTTGGCATCAGTAAGAACAGTCAAGAGTCCCAGGGCAGGGCCACACTTCTC
30 CCATCTTTTCGCTTCCACCCAGCTTGTGATCGCTAGCCTCCAGAGCTCAGCTGCCATTAAGTCCCCATG
CACGTAATCAGTCTCCACACCCAGTTTGGGGAACATAACCCCTTGATTGAAGTGTTTTTCCCTCCGCT
CCCATGGAAACCATGCTGCCTGCCCTGCTGGAGCAGACGGCCACCTCCATAGATGCAGCCCTTTCTTTCC
CGTCTTCGCCCTGTTACGTTGTAGTTGGATTTGTCTGTTTGTCTGGGTTCCACAGAGTGAATATGATAGT
GAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAG
35 GTATCTTGAATATTTGTCAAAAGGTTCTAGCCACCACGTCATGGAGAGTCTGGATATCTCCTTCCCTGA
CGTGGCTCCAGGCCAGTGCAGTGTAACTGCTGGGACATCCCATGTTTTGAAGGGTTTTCTTCTGCATCT
GGGACCTCACAGACACTGGATTGTGACATTGGAGGCTCTGTGACATTGGAGGTCAATGGCATTTGGCCAAAG
CCTGAAGCACAGGACAGCTAGAGGCAGCAGGCTCCGAGTGCCAGGGAGAGCTTGTGGCTGGCCTGTTTT
GTATGAAGATGGTCTTTCTGATCACGACTTCAAATCCCACAGTAGCCCTGAAAGACATCTAAGAACTCC
40 TGCATCACAAGAGAAAAGGACACCAGTACCAGCAGGGAGAGCTGTGACCCTAGAAATTCCATGACGACCC
AGTAGATATCCTTGGGCCCTCTCCAAGCCTGGGCCCTTTTCCCATAGAGTTTGGGATGGACTGTCCCACT
GATGAAGGGGACATCTTAGGAGACTCCCTTGGTTTCCAAGCTGTCAGCCCCCTGAACTTGCACGACCTCC
TACAGCTTCAGGGACTAGGCCTTTTGAAGATTAGGAACCTCAGGCCACATCAGCCACTTCTGATGTACAG
45 TTAAGGACAATGTGGAGACTAGGAGGAAGCAGCCAGCCCTTTCCCATTAAGAACTCTTGAGTGGCCAGGG
CTACCTATTGTGAGCTTCCCACTGATAAGACTTTAGCTGTCCATAGAAGTGAAGTCCGAGGGAGGAAAAG
TGTGGTTTCTTCATCATGGTTACCTGTGCTGGTTCTCTCTTACACCCATTACCCATCCCGCAGTTCC
TGTCCTTGAATGGGGGTGGGGTGTCTGCCTATCTCTTGTGGGGTGATCAGCCCCAAAATCATGATTTG
GAGTGTATCTGATCAGTGTGATAGGCAGTTTACAAAGGGATTCTGGCTTGTGACTTCAGTGAGGACAATC
50 CCCAGGGCCCTTTCTTCCATGCCTCTCCAACCTCAGAGCCAATGTCTTTGGGTGGGCTAGATAGATAGG
GCATACAATTGGCCTGGTTCTTCCAAGCTCTTAATTCACCTTTATCAATAGTTCCATTTAAATGACTTCA
ATGATAAGAGTGTATCCATTTGAGATTGCTTGCCTTGTGGGGAGGGGAGGAGGAACACATTAAGATA
45 ATTCACATGGGCAAAGGAGGTCTTGGAGTGTAGCCGTTAAGCCATCTTGTAAACCCATTTCATGATTTG
ACCACCTGCTAGAGAGAAGAGGTGCCAAGAGACTAGAATTTGGAGGCTTGGCTGTCCCACTAATAGGCTT
TCGCAAGGCAGAGGTAGCCAGCTAGTCCCTGCCCTCCCAGCCAGGTACAGCTCTCAGGTTTGTGGAGGT
AATCTGTGAACCTTCTTCTGCTGCCTTCTTGTGATGTCCAGAGCCACAGTCAAATACCTCCTAAGAA
55 CCCTGGCTTCCCTTCCCTCTAATCCACTGGCACATGACTATCACCTCTGGATTGACCTCAGATCCATAGCC
TACACACTGTAGCAGTGGCCAAGATCACTTCTTTATCTCCATCTGTTCTGTTCTCCAGGAAAGTAAGT
GGGGATGAGGGTGGAGGTGGTAATCAACTGTAGATCTGTGGCTTATGAGCCTTCAGACTTCTCTCTGGC
TTCTTCTGGAAGGGTTACTATTGGCAGTATTGCAATCTCACCCCTCTGATGAAGTGTAGCCTGTGCCGTT
ACTGTGCTGGGCATGATCTCCAGTGTGCAAGTCCCATGATTTCTTTGGTGATTTTGGGGTGGGGGA
60 GGGACACAAATCAGCTTAGCTTAGCTTCCGTGTCTGTGAATGTCCATATAGTGTATTGTGTTTAAACAAAT
GATCTACACTGACTGTTGCTGTAAAAGTGAATTTGAAATAAAGTTATTACTCTGAATAAAAAAAAAA
AAAAA

SEQ ID NO:6
>Reverse Complement of SEQ ID NO:5
TTTTTTTTTTTTTTTTTTTATTTCAGAGTAATAACTTTATTTCCAAATTCACCTTTTACAGCAACAGTCAGTGTAGATC

ATTGTGTTAAACACAATACACTATATGGACATTACAGACAGGAAGCTAAGCTAAGCTGATTGTGTCCCT
TCCCCCACCCTCAAAATCACCAAAGAAATCATGGGACTTGCAAGCACTGGAGATCATGCCAGCACAGT
AACGGCACAGGCTACAGTTCATCAGGAGGGTGAGATTGCAATACTGCCAATAGTAACCCTTCCAGAAGAA
GCCAGAGAGAAGTCTGAAGGCTCATAAAGCCACAGATCTACAGTTGATTACCACCTCCACCCTCATCCCC
5 ACTTACTTTCTGGAGAACAGAACAGATGGAGATAAAGGAAGTGATCTTGGCCACTGCTAGCAGTGTGTA
GGCTATGGATCTGAGGTCAATCCAGAGGTGATAGTCATGTGCCAGTGGATTAGAGGGAAGGAAGCCAGGG
TTCTTAGGAGGTATTTGACTGTGGGCTCTGGACATCACAAGAAGGCAGCAGGAAGAGAAGTTCACAGATT
ACCTCCACAAACCTGAGAGCTGTACCTGGCTGGGAAGGCAGGGACCTAGCTGGCTACCTCTGCCTTGCGA
10 AAGCCTATTAGTGGGACAGCCAAGCCTCCAAGTTCTAGTCTCTTGGCACCTCTTCTCTAGCAGGTGGT
CAAAATCATGAATGGGGTTACAAGATGGCTTAACGGCTACACTCCAAGACCTCCCTTTGCCCATGTGAAT
TATCTTAATGTGTTCCCTCCCTCCCCCTCCCCACACGCAAGCAATCTCAAAATGGGATACACTCTTATCAT
TGAAGTCAATTTAAATGGAACATTGATAAAGTGAATTAAGAGCTTGGAGGAACAGGCCAATTGTATGC
CCTATCTATCTAGCCACCCAAAGACATTGGCTCTGAGTTGGAGAGGCATGGAAAGAAAGGGCCCTGGGG
15 GATTGTCCCTCACTGAAGTCAAGCCAGAATCCCTTTGTAAACTGCCTATCAGCACTGATCAGATCACTC
CAAATCATGATTTTTGGGCTGATCACCCACAAGAGATAGGCAGAGCACCCCAACCCCATCAAGGACA
GGAAGTGGGGATGGGTAAATGGGTGTAAGAGAGAGAACCACGACAGGTAACCATGATGAAGAAACCACA
CTTTTCTCTCCCTCGGACTCACTTCTATGGACAGCTAAAGTCTTATCAGTGGGGAAGCTCACAAATAGGTAG
CCCTGGGCACTCAAGAGTTCTTTAATGGGAAGGCTGGCTGCTTCTCCTAGTCTCCACATTGTCTCTAA
20 CTGTACATCAGAAGTGGCTGATGTGGGCTGAGGTTCCTAATCTTCAAAGGCCTAGTCCCTGAGGTCTGA
GGAGGTCTGTGCAAGTTTCAAGGGGCTGACAGCTTGGAAACCAAGGGAGTCTCCTAAGATGTCCCTTATC
AGTGGGACAGTCCATCCCAAACCTCTATGGTGAAGGAGGCTGGAGAGGGCCCAAGGATATCTACT
GGGTCTCATGGAATTTCTAGGGTACAGCTCTCCCTGCTGGTACTGGTGTCTTTTCTCTGTGATGCA
GGAGTTCTTAGATGTCTTTCAGGGCTACTGTGGGATTTGAAGTCGTGATCAGAAAGGACCATCTTCATAC
25 AAAACAGGCCAGCCACAAGCTCTCCCTGGCACTCGGAGCCTGCTGCCTCTAGCTGGTCTGTGCTTCAGG
CCTTGGCCAATTGCCATTGACCTCCAATGTACAGACCTCCAATGTCAATCCAGTGTCTGTGAGGTCCC
AGATGCAAGAAGAAACCCTTCAAAACATGGGATGTCCAGCAGGTTAGCACTGCACTGGCCTGGAGCCACG
TCAGGAAGGAGATATCCAGACTCTCCATCACGTGGTGGGCTAGAACCTTTTGACAAATATTTCAAGATAC
ATGCGTCTTTTTTTTTTCTTTTTCTTTTTCTTTTTTTTTTTTTTTTTTCTTTTTCTTTCTTTCTTTT
30 ACTATCATAGTCACTCTGGTGAACCCAGACAAACAGACAAATCCAACACGTAACAGGGCGAAGACG
GGAAAGAAAGGGCTGCATCTATGGAGGTGGCCGTCTGCTCCAGCAGGGCAGGCAGCATGGTTTCCATGGG
ACCGGAGGAAAAAACACTTCAATCAAGGGGGTATGTTCCCAAACCTGGGGTGTGGAGACTGATTACGTG
CATGGGCACTTAATGGCAGCTGAGCTCTGGGAGGCTAGCGATCACAAGCTGGGGTGAAGCGAAAGATGG
GAGAAGTGTGGCCCTGCCCTGGGACTCTTGACTGTTCTTACTGATGCCAAGACATTGGCACCTGACTTGG
35 CTGCCTCCAGCTCAACACAAGGAGTCAGGCCTAGGAGGCATCCACTTAGATAAAAGAAAAGGCAGAGGTC
CAAGGTCAATCCCAAGGCAGGCACACACACAGTTCCTCATCCAGGATAGGAAGTAAATGGAGTGAACCAACAA
GGTCGTAAGGTTCTTTGTGGGAGGCACACTGGTTGGATTCTGGAACGTAGGACTAGAGACTGAGGCCCCA
AATCTTTGCTTCCCTGGACTCCAACCCCTAGTGTAGAGCAGATATTGCCCATATCTACCCAGGGCCAG
GGATGGGGCTGGGAGAGGCATGGCACTCAGGACAGTGAACGTCATGTACGGACGGCAGTGACTAGCTC
40 TCGTGGCAGACGTGGGCATGATAGGACAGAGAGGGGATACAGTGGCTGTGTGAGGGATGGGAGGCCCTG
GGACCCACATCCAGAAATACCACCCCCATCCCTCCCACTACAGAAGTGCCAGAGGGCCAAAGCATGAGAA
CAGGCAGAGGTCCCCAAGAGGCACAAGTCTTACAAAGATCTGGTTAGCCCTAAAGTCCCAGGTCTGTA
ATGGTGGCCAAATCATGGCTGTAGTTCCAAACTTGAGAACTCAGTAAAGCAGCTTTTCTGTGGGAGCGA
AGGGAAACACACTCGCTCAGGACCTCCACCTTGGGGGAGGGAGGAAGAAGCCAGTGCCCTGGGATGTCA
45 AGAGCAGCCTTCAAGAGAACCAATCTACAAGGTACCACCTGCTGGCTTACCTTCTGCCCCAATACCC
CTTCTCCACAGGCTGCCCTGCAGAAGGGGCACACACACCCACGTTACCCCAAGTGTCTTATCAAGCA
GGCATCTGAGCTAGCTAGGACTGCTGCAGGCAGCTGCAGCACCTGTCTCTCCCAAGCTACTTGGCAAGG
AGCCAGTGTCCCTCTCCCAACCTGCCTTCTCTACCTCTGTCTCTAACTCAGTCCACCCATCCATCTCT
CAGCCTTCGCTGTGCTGTTTTCAGTCCCCACTCACACCCACACAAGTTAACAGCACCTGCCTACGGCCCC
ACGAACACACCAAGTCAAAATCTCTCATTGCTGCCACTGTCCCTGAAGCCCCTAGGATGGGGCTATGGG
50 CAATTAGCTGCCCTAGTCCCTCAGCCACTCCCCAGAAGCAGCTCCAGAGCCTTCTTACCCCTCAATAC
TCAGAGAGGGAGGGCGGGTCAAGGGGGGAAATCAATTAGCAATTGCCAAGGAAATTTTTTGGCCATG
TTTTTACATGTTTTTTTTTCCCTTAAATATGTTTTATTTTTAGCCCAAAATCAATTTGGAAAGATGAAA
TGTACTTTTCCCATCACTGATTTTGAAGTCCCGAGCCAAATCCGAGCCACAAAAGCAGGTAGGTGACAA
GCAGGTGAGCCTGTCTATGAGGAGCAGCGGGGAGGGCAGAGGGCAAGGGCCAGATCATCTTTTTTTTT
55 TTTTTTTCCACACTCTCACTCTCTCTCTCTCCATGATTATTGACTGCCCTGGGAGCCTGATCACAAC
CCTGCTTGGCCAAGGAAGCAGACACTTCATCGGCTAGTGTGGCAAGCTGTGGTGAGTCCACCATGTCTGAT
GCTGCCGTGGAAGACACATTGCTGAGGTGCCGTGGAGATGTGTCCCCAGACACCACGGGTGACTTATAC
ACAATTTCTGCTCCATGGTCTGTCTTGGCTTTGGCATTCTCCCTGAAGGTGAGCTTGTGGGTTTCAATCT
TCTTATTTCCCTCCTCCAGGGACGTGGGTGATATTATCAAGGAGCCAACTTTCGACTGGACTCTGTCTT
60 GAAGTCCAGCTTCTCTGATTTTACTTCCACCTGGCCACCTCTGGCTTGTGATGGATGTTCCCTAACGAG
CCACACTTGGAGGTCACTTTGCTCAGGTCCACCGGCTTGTAGACTATTTGCACACTGCCTCCACCCGGGA

CGTGTTTGATATTATCCTTCGAGCCACACTTGGACTGGACGTTGCTAAGATCCAGCTTCTTATTAATTAT
 CTGCACCTTGCCACCTCCTGGCTGGTGTCTCAGGTTCTCAGTAGAGCCAATCTCGACCTGACATTCTTT
 AGGTCTGGCATGGGCACAGGGGAGTCTGCAGGCGGCTCTTACTAGCTGATGGTGAAGTATAGGGGAGTGC
 GGACCACTGCCACCTTCTTGGGCTCCCGGGTGGGCGGTGTTGGTAGGGATGGGGTGGCGAGCGACTGCC
 5 AGGCGTTCCGGGAGAGCCGGGGCTGCTGTAGCCGCTTCGTTCTCCGGATTTTGGTGGTTCACCTGACCCT
 GGAGGAGTCTTAGGGCTGGGCGTGGTCTTGGCCGGATCCTGGTGGCGTTGGACGTGCCCTTCTGGGCGG
 GAGAGGCTGCTCCCCGAGGTGTGGCGATCTTCGCCCGGTTTTGCCATCAGCGCCCTTGGCTTCTTCTC
 GTCATTTCTGTCTCTTTGCTGGCCACACGAGCTTGAGTCACATGCCAGCGGCTTGGTCTCTCTGG
 10 TTCGGGGTGTCTCCGATGCCTGCTTCTTCGGCTGTAATTCCTTCTGGGATCTCCGTGTGGGGCTGGGCAG
 CGGCTGCTTGTGGGAGCTCTCTCATCCACTAGGGGCGCAGTCACGTCTTCAGCAGTTGGAGTGTCTT
 AGCATCGAGGTCTCCGACCCTGGTTCCTCCGCTCCATCATCGCGGGGGGCTGTGGGGGAGACTCTTTT
 AAGCCATGGTCCATGTCTCCTTCTTGGTCTTGGAGCAGAGTGTAACTCTCCAGCATGGTCTTCCATTGTGT
 CAAACTCTGGCGAGGGTCAGCCATACTGGTTCAAAGCCTGATAATCGACAGAAGGCGAGGACAGAAGAG
 15 GACAGCGGAGGAGAAGGTGGTTGTGGCGGCGGGCGCAGAAAGGTGGGCGGTGGCGGCGGGCGCTGTCTGG
 TGCTGGAGCTGGTGGGTGGCGGAGACTGAGAGCGCGCGGGCCGAGAAAGCGCTTCTGGAGGCCGGCGG

SEQ ID NO:7

>XM_005584540.1 PREDICTED: *Macaca fascicularis* microtubule associated
 protein tau (MAPT), transcript variant X13, mRNA
 20 GCCGAGCGGCAGGGCGCTCGCGCGCGCCACTGGTGGCCGGAGGAGAAGGCTCCCGCGGAGGCCGGGCTG
 CCCGCCCCCTCCCTGGGGAGGCTCGCGCTCCCGCTGCTCGCGCTGCGCCGCTGCGCGGCTCGGGAAC
 GCGCCCTCTTCCCCGGCGCGCGCCCTCGCAGTCACCGCCACCCACCAGCTCCGGCACCAACAGCAGCGCC
 GCTGCCACGCGCCACCTTCTGCGCGCGCCACCACAGCCACCTTCTCCTCCTCCGCTGTCTCTCCCGTCC
 TCGCCTCTGTCGACTATCAGGCGAGCCTTGAACAGGATGGCTGAGCCCCGCCAGGAGTTCGATGTGATG
 25 GAAGATCACGCTGGGACGTACGGGTGGGGGACAGGAAAGATCAAGAGGGCTACACCATGCTCCAAGACC
 AAGAGGGTGACACGGACGCTGGCCTGAAAGAATCTCCCTGCAGACCCCGCTGAGGATGGATCTGAGGA
 ACTGGGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACGGCGGAAGATGTGACAGCGCCCTTAGTGGAT
 GAGAGAGCTCCCGGCGAGCAGGCTGCCGCCAGCCCCACATGGAGATCCCAGAAGGAACCACAGCTGAGG
 AAGCAGGATCGGAGACACCCCGAGCTGGAAGACGAAGCTGTGGTACAGTGACCCAAGCTCGCATGGT
 30 CAGTAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGGGGGCTGATGGGAAAAACGAAGATC
 CCCACACCCCGGGGAGCGGCCCTCCAGGCCAGAAGGGCCAAGCCAACGCCACCAGGATTCCAGCAAAAA
 CCCCGCCCGCCCCAAAGACACACCCAGCTCTGGTGAACCTCCAAAATCAGGGGATCGCAGTGGCTACAG
 CAGCCCCGGCTCCCCGGGCACTCCCGGCAGCGCTCCCGCACCCCGTCCCTTCCAACCCCTCCAGCCCCG
 35 GAGCCCAAGAAGGTGGCGGTGGTCCGTACTCCACCTAAGTCGCGCTCTTCCGCCAAGAGCCGCTGCAGA
 CAGCCCCGCTGCCATGCCAGACCTGAAGAAGCTCAAGTCCAAGATCGGCTCCACCGAGAAGCTGAAGCA
 CCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGT
 GGCTCAAAGGATAATATCAAACACGTCCCGGGAGGCGGCAGTGTGCAAAATAGTCTACAAACAGTTGACC
 TGAGCAAGGTGACCTCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGGAGGTGGCCAGGTGGA
 40 AGTAAATCTGAGAAGCTGGACTTCAAGGACAGAGTGCAGTCAAGATCGGGTCCCTGGACAATATCACC
 CATGTCCCTGGCGGAGGAAATAAAAAAGATTGAACCCACAAGCTGACCTTCCGCGAGAACGCCAAAGCCA
 AGACAGACCACGGGGCGGAAATCGTGTACAAGTCCCGGTGGTGTCTGGGGACACGTCTCCACGGCACCT
 CAGCAATGTCTCCTCCACCGGCAGCATCGACATGGTAGACTCGCCCCAGCTCGCCACGCTAGCCGACGAG
 GTGTCTGCCTCCCTGGCCAAGCAGGGTTTGTGATCAGGCCCCGGGGCGGTCAATAATCTGGAGAGAAG
 45 AGAGAGTGAGAGTGTGAAAAAAGAAATAATGACCCGGCCCCGCTCTGCCCCAGCTGCTCTCTCGC
 AGTTCCGTTAATCGGTTTCACTTAACCGGCTTTTATCGCTCGGCTTTGGCTCGGGACTTCAAATCAG
 TGATGGGAATAAGAGCAAATTGCATCTTTCAAATTGATCGGTGGGCTAATAATAAAATATTTTTTAAAA
 AACATTCAAAAACATGGCCACACCAACATTTCTCGGGCAATTCTTTTGTATCTTTTTTTTCCCCCT
 CCATGTAGAAGAGGGAGAAGGAGAGGCTGTGAAAGCTGCTTCGGGGGGATTTCAGAGACTGGGGGTGCC
 50 CACCGCTCTGGCCCTGTCTGGGGGTGTCTACAGAGGACAGCGGCAGCAACAAAGGATTTGAAACTTGGTG
 TGTTCTGTGGAGCCACAGGCAGACGATGTCAACCTTGTGTGAGTGTGACGGGTGGGGGTGGGCGGGAGGC
 CATGGGGGAGGCCAAGGCAGGGGCTGGGCAGAGGGGAGAGGAAGGACGAGAAGGGGGAGTGGGAGAGGAA
 GCCACATGCTGGAGAGGAGATGCCCTCCTCCGCGCCACTGGGAGGGCCAAGGCTCCGCCACCTGCAGTG
 TCTCAGACTGAGCGGCTGCCTGTCTTGGTGGCCAGGGTCTGCTGCGAGTTGATGTGCCACCCCTCTGCAG
 55 GGCAGCCTGTGGGAGAAGGGGCGGGGTAAGAAGAGAAGGCAAGCTGGCGGGAGGGTGGCACCCCGTGG
 ATGACCTCCTTGAAAAAGACTGACCTTGATGTGCGAGGGCGCTGGCCTCTTCTCCCTCCCTGCAGGGTA
 GGGGGCTGAGCCGAGGGGCTTCCCTCTGCTCCACAGAAACCTGTTTTATTGAGTTCTGAAGGTGGAA
 CTGCAGCCATGATTTTGGCCACTTTGCAGACCTGGGACTTTAGGGCTAACCAGTTCTCTTTGTAAGGACT
 TGTGCCTCTTGGGAGAGTCCACCCGTTTCCAAGCCTGGGCCACCGGCATCTTGGAGTGTGCAGGGGTG
 60 TGGGAGGCGGGTCCCGAGCCCCCTGTCTTCCACGGCCACTGCAGTACCCCTGTCTGCCCCACTGTGC
 TGTCTGTGCCATGAGAACCAGTCACTGCCTATACCCCTCATCAGTCACAATGTCAAATTTCCAGCC
 TCACCACCCCTTCTCAGTAAGGACCTGGTTGGCTGTGGGAGGCACCTACTCCATACTAGGGGTGAAA

TTAAGGGAAGGTAAAGTCCAGGCACAAGAGTGGGACCCAGCCTCTCACTCTCAGTTCCACTCATCCAAC
TGGGTCCCTCACCACGAATCTCACGACCTGATTTCGGTTCCCTGCCTCCTCCTCCCATCACAGATGTGAGC
CAGGGCACTGCTCAGCTGTGACCCTCGGTGTTCCTGCCTTGTGACATAGAGAGAGCCCTTTCCCCCGA
GAAGGCCCTGGCCCCCTTCTGTGCTGAGCCCGCAGCAGGAGGCTGGGTGTCTGGTTGTGGTGACGGCAC
5 CAGGATGGGCGGGCAAGGCACCCAGGGCAGGCCACAGTCCCGCTGTCCCCCACTTGCACCCAGCTTGT
GGCTGCCAGCCTCCCAGACAGCCAGCCGCTGCTCAGCTCCACATGCATAGAATCAGCCCTCCACATCC
CAAAAAGGGGAACACACCCCTTCGAAATGGTTTTCTCCCCGGTCCCAGCTGGAAGCCATGCTGTCTGTT
CTGCTGGAGCAGCTGAACATATACATAGATGTTGCCCTGCCCTCCCCATCTGCACCCCTGTTGCGTTGTAG
10 TTGGATTGTCTGTTTATGCTTGGATTACACAGAGTGAATGATAGTGAAGAAGAAAAAAAAAAAAAAAA
AAAGGACGCATGTATCTTGAAATGCTTGTAAGAGGTTTCTAACCACCCCTCACAAGGTGTCTCTCACC
CCACGCTGGGACGCTGTGGCCTGTGTGGCGCCGCCCTGCTGGGGCCTCCCAGGTTTGAAAGGCTTTCC
TCAGCATCCGGGACCCAAACAGAGACCAGATTCTAGCATCTAAGGAGGCCGTTTCACTGTGAAGAAGGCCT
GAAGCACAGGATTAGGACTGAAGCGATGACATCTCTTCCCTACTTCCCCTTGGGGCTCTCTGTGTGAGG
GCAGAGATAGTCTTGTGGCTGGTCTGGCTTGGCGCACGAGGATGGTTCTCTGTGTCACAGCCGGAAG
15 TCCACAGCAGTCTTAAAGGAGGCTTACAACCTCTGCATCACAAGAAGAAGGAAGCCAGTGCCAGCTGGG
GGGATCTGCAGCTCCCAGAAGCTCCATGAGCCTCAGCCACCCCGCAGACTGGGTTCCTCGCCAAGCTCGC
CCTCTGGAGGGGAGCCAGCCTCCCACCAAGGGCCCTGCGACCACAGCAGGGATTGGGATGAATGGCCTA
TCCTGGATCTGCTCCAGAGGCCGAGCCACCTGCCGTGAGGAAGGATAAGTCAGGAGACACCGTTCCCAA
GCCTTGACCAGAGCACCTCAGCCCACTGACCTTGACAAAACCTCCATCTGCTGCCATGAGAAAAGGGAAGC
20 CCGCTTTGCAAAAAAATGCTGCCCTAAAGAACTCAGCAGCCTCAGGCTCAATTCTGCCGCTTCTGGTTT
GGTACAGTTAAAGGCAACCCCTGAGGGACTTGGCAGTAGAAATCCAGGGCATCCCTAGGGCTGGCAACTT
CGTGTGCAGCTAGAGCTTTCCTGCAAGAAGTTTCTGGGCCCAGAACTCTCCACCAGGAAGCTCCCTGCT
GTTTCGCTAAGTCCCAGCAATTCTCTAAGTGAAGGGATCTGAGAATGAGGAGGAAATGTGGGGTAGAGATT
TGGTGGTGGTTAGAGACATGCCCCCTCATTACTGCCAACAGTTTGGGCTGCATTTTACGTACCTCGG
25 TTCCTCTTCTGAGTTCTTGTGGCTGCTCTTCCAGCACCCTGGGCTTATCCGGTAGGCTCTGGGATCT
CCCCCTTGTGGGGCAGGCTCTTGGGGCCAGCCTAAGATCATGGTTTAGGGTGATCAGTGTGTCAGATAA
ATTGCAAGGCACGCTGGCTTGTGACCTCAAATGACAATCCCCCAGGGCTGGGCACTCTCCCTCCCC
TCACTTCTCCACCTGCAGAGCCAGTGTCCGTGGGTGGGCTAGATAGGATATACTGTATGCCGGCTCCTT
CAAGCTGTTGACTCACTTTATCAATAGTTCCATTTAAATTGACTTCAATGGTGAGACTGTATCTCTGTTT
30 CTATTGCTTATTGTGCTATGGGGGGAGGGGGGAGGAATGTGTAACATAGTTAATAGGTTAAAGGGAGAT
TTGGGGTGCAGCACTCAATTGGCTCGTAACCCCTTTTCAATCACTTCAACCACATTTGCTAAAGGGAGG
AGCAGCCACGCGTTAGAGGCCCTTGGGGTTTCTCTTTTCACTGACAGCCTTTCCAGGCAGCTGGCCA
GTTCCCCATTCCCTCCCCAGCCAGGTGCAGGCGTAGCAATATGGACATCTGGTTGCTTTGGCCTGCTGCC
CTCTTTAGGGGTCTTAAAGCCACAATCATGCCTCCCTAAGACCCTGGCATCCTTCTTTTAAAGCCGTTG
35 GCACCTCTGTGCCACCTCTCACACTGGCTCCAGACACAGCCTGTGCTTCTGGCAGCTGAGATCACTCACT
TCCCCCTCCTCATCTTTGTTGGAGCTCCAAGTCAAGCCACGAGGTGAGGGCAGGGCAGAGGTGGTCACC
AGCGTGTCCCATCTACAGACCTGTGGCTTCGTAAGACTTCTGATTCTCTTCACTTTGAAAAGGGTTAC
CCTGGGCACTGGCCTAGAGTCTCACCTCCTAATAGACTTACCCCATGAGTTTGCCATGTTGAGCAGGAC
AATTTCTGGCACTTGCAAGTCCCATGATTCTTCTCGGTAATTGTGAGGGTGGGGGAGGGACATGAAATCA
40 TCTTAGCTTAGCTTCTGTCTGTGAATGTCTATATAGTGTATTGTGTGTTTAAACAATGATTTACACTG
ACTGTTGCCGTAAAAGTGAATTTGAAAATAAGTTATTACTCTGATTAAA

SEQ ID NO:8

>Reverse Complement of SEQ ID NO:7

TTTAATCAGAGTAATAACTTTTATTTCCAAATTCACCTTTTACGGCAACAGT
45 CAGTGTAATCATTTTGTAAAACACACAATACACTATATAGACATTCACAGACAGGAAGCTAAGCTAAGA
TGATTTTCATGTCCCTCCCCCACCCTCACAATTACCGAAGAAATCATGGGACTTGCAAGTGCCAGAAATT
GTCTGTCTCAACATGGCAAACCTCATGGGGGTAAGTCTATTAGGAGGTGAGACTCTAGGCCAGTGCCAGG
GTAACCCCTTTTCAAAGCTGAAGAGAAATCAGAAGTCTTACGAAGCCACAGGTCTGTAGATGGGACACGCT
50 GGTGACCACCTCTGCCCTCGCCCTGACCTCGTGGCTTGACTTGAGCTCCAACAAGATGGAGAGGGGGA
AGTGAGTGATCTCAGCTGCCAGAAGCACAGGCTGTGTCTGGAGCCAGTGTGAGAGGTGGCACAGAGGTGC
CAACGGCTTAAAAGGAAGGATGCCAGGGTCTTAGGGAGGCATGATTGTGGGCTTAGGACCCCTGAAAGAG
GGCAGCAGGCCAAAGCAACCAGATGTCCATATTGTACGCTGCACCTGGCTGGGGAGGGGAATGGGGAAC
TGGCCAGCTGCCTGGGAAAGGCTGTCACTGGAAAGAGAAACCCCAAGGGCTCTAACCCTGGCTGCT
55 CCTCCCTTTAGCAAAATGTGGTTGAAATGATGAAAAGGGTTACGAGGCAATTGAAGTGCTGCACCCCAAG
ATCTCCCTTTACCATGTAACTATGTTACACATTCTCCCCCTCCCCCATAGCACAATAAGCAATAG
CAAACAGGATACAGTCTCACCATTGAAGTCAATTTAAATGGAATATTGATAAAGTGAGTCAACAGCTTG
AAGGAGCCGGCATACAGTATATCCTATCTAGCCACCCACGGACACTGGCTCTGCAGGTGGGAGAGTGA
GGGGAGGGGAGGAGTGGCCAGCCCTGGGGGGATTGTCAATTTAGGTCACAAGCCAGCGTGCCCTTTGCAAT
60 TTATCTGCCAGCACTGATCACCCTAAACCATGATCTTAGGCTGGCCCCAAGAGCCTGCCCCACAAGGGG
AGATCCAGAGCCTACCGGATAAGGCCACGGTGTGAAGAGCAGGGCACAGAAGCTTCAGGAAGAGGAA

CCGAGGTACGTGAAAAATGCAGCCGAAACTGTTGGCAGTAATGAGGGGGGCATGTCTCTAACCACCACCA
AATCTCTACCCACATTTCTCTCTATTCTCAGATCCCTTCACTTAGAGAAATGCTGGGACTTAGCGAAC
AGCAGGGAGCTTCTGGTGGAGAGTTCTGGGCCAGAACTTCTGCAGGGAAAGCTCTAGCTGCACACG
AAGTTGCCAGCCCTAGGGGATGCCCTGGATTTCTACTGCCAAGTCCCTCAGGGTTGCCTTTAACTGTACC
5 CAAACCAGAAGCGGCAGAAATTGAGCCTGAGGCTGCTGAGTTTCTTAGGCAGCAATTTTTTGCAAAGGCG
GCTTCCCTTTTCTCATGGCAGCAGATGGAGTTTGTGCAAGGTCAGTGGGCTGAGGTGCTCTGGTCAAGGC
TTTGGGAACGGTGTCTCTGACTTATCTTCTCAGGCAGGTGGCTCGGGCTCTGGAGCAGATCCAGGA
TAGGCCATTTCATCCCAATCCCTGCTGTGGTCGCAGGGCCCTTGGTGGGAGGCTGGCTGCCCTCCAGAGG
10 GCGAGCTTGGCGAGGAACCCAGTCTGCGGGGTGGCTGAGGCTCATGGAGCTTCTGGGAGCTGCAGATCCC
CCCAGCTGGCACTGGCTTCTTCTTCTGTGATGCAGGAGTTGTAAGCCTCCTTTAGGACTGCTGTGGGA
CTTCGGGCTGTGACCAGAGAGAACCATCCTCGTGCCGCAAGCCAGACCAGCCACAAGACCTACTCTCTGC
CCTGACACAGAGAGCCCCAAGGGGAAGTAGGGAAGGAGATGTCATCGCTTCAGTCCTAATCCTGTGCTTC
AGGCCTTCTTCACAGCTGAACGGCCTCCTTAGATGCTAGAATCTGGTCTCTGTTGGGTCCCGGATGCTGA
GGAAAGCCTTTCAAACCTTGGGAGGCCCCAGCAGGGCGGCCACACAGGCCACACGCTCCCGAGCGTGG
15 GGGTGAGAGACACCTTGTGAGGGTGGGTAGAAACCTCTTTACAAGCATTTCAAGATACATGCGTCTCTT
TTTTTTTTTTTTTTTTTCTTTTCACTATCATAGTCACTCTGGTGAATCCAAGCATAAACAGACAAATCCAA
CTACAACCAACAGGGTGCAGATGGGGAGGGCAGGGCAACATCTATGTATATGTTTCAGCTGCTCCAGCAG
AACAGACAGCATGGCTTCCAGCTGGGACCGGGGAGAAAACATTTCAAGGGGGTGTGTTCCCTTTTTTG
GGATGTGGAGGGGTGATTCTATGCATGTGGAGCTGAGCAGCGGGCTGGGCTGTCTGGGAGGCTGGCAGCC
20 ACAAGCTGGGGTGCAAGTGGGGGACAGCGGGACTGTGGGCCTGCCCTGGGTGCCTTGCCCGCCCATCCTG
GTGCCGTACCGACAACCAGGACACCCAGCCTCCTGCTGCGGGCTCAGCACAGGAAGGGGCCAGGCCTTC
TCGGGGGAGAAAGGGCTCTCTCTATGTCAACAAGGCAGAAACACCGAGGGTACAGCTGAGCAGTGCCCTG
GCTCACATCTGTGATGGGAGGAGGAGGCAGGGAACCGAATCAGGTCTGTGAGATTCGTGGTGAGGGACCCA
GTTGGATGAGTGGAACTGAGAGTGAGAGGCTGGGTCCCCTCTTGTGCTGGACTTTACCTTCCCTTAA
25 TTTACCCCTCAGTATGGAGTAGGTGCCTCCCACAGCCAACCAGGGTCTTACTGAGAAGGGGGGTGGTGA
GGCTGGGAATTTGGACATTTGTGACGTGATGAGGGGTATAGGCAGTGAAGTGGTCTCATGGCAGACAGCA
GCACAGTGGGGCAGACAGGGGTGACTGCAGTGGCCGTGGGAAGGACAGGGGGCTCGGGACCCGCCCTCCCA
GACCCCTGCACACTCCAGAGATGCCGGTGGCCAGGCTTGGAAACGGGTGGACGTCTCCCAAGAGGCACA
AGTCCTTACAAAGAGAACTGGTTAGCCCTAAAGTCCCAGGTCTGCAAAGTGCCAAAAATCATGGCTGCAG
30 TTCCAACCTTCAGAACTCAATAAAACAGGGTTTCTGTGGAGCAGAGGGAAGCCCTCGGCTCAGGCCCC
TACCTGTGAGGGGAGGGAAGAGGGCCAGCGCCTCCGACATCAAGGTCACTTTTCCAGAGGTCAT
CCACGGGGTGCCACCCCTCCCGCCAGCTTGCCTTCTCTTACCCGCCGCCCTTCTCCACAGGCTGCC
CTGCAGAGGGTGGCAGATCAACTCGCAGCAGACCTGGCCACCAAGGACAGGCAGCCGCTCAGTCTGAGA
CACTGCAGGTGGCGGAGGCCTTGGCCCTCCAGTGGCGCGGAGGAGGCATCTCTCTCCAGCATGTGGC
35 TTCTCTCCCACTCCCCCTTCTCGTCTTCTCTCTCCCTCTGCCCAGCCCCTGCTTGGCTTCCCCCATG
GCCTCCCGCCCCACCCCTCACACTCACACAAGGTTGACATCGTCTGCCTGTGGCTCCACGAACA
CACCAAGTTTCAAATCCTTTGTTGCTGCCGCTGCCCTGTGTGACACCCCCACGACAGGGCCAGAGCGGTG
GGCACCCCCAGTCTCTTGAAATCCCCCGAAGCAGCTTTACAGCCTCTCCTTCTCCCTCTTCTACATGG
AGGGGGAAAAAAGAAATCAAAAGGAATTGCCGAGGAAATGTTGGGTGTGGCCATGTTTTTGAATGTT
40 TTTTAAAAAATATTTTATTATTAGCCACCGATCAATTTGGAAGATGCAATTTGCTCTTATTCCCATCA
CTGATTTTGAAGTCCCGAGCCAAAGCCGAGCGATAAAAGCCGGTTAAGTGATGAACCGATTAAACCGAAT
CGGAGGAGCAGCTGGGGCAGAGGGCGGGGCGGGTCAATTATCTTTTTTTTCCACACTCTCACTCTCT
CTTCTCTCCAGATTATTGACCGCCCGGGGGCTGATCACAAACCCCTGCTTGGCCAGGGCAGACAC
CTCGTGGCTAGCGTGGCGAGCTGGGGCAGTCTACCATGTGATGCTGCCGTGGAGGAGACATTGCTG
45 AGGTGCCGTGGAGACGTGTCCCAGACACCACGGCGACTTGTACACGATTTCCGCCCGTGGTCTGTCT
TGGCTTTGGCGTTCTCGCGGAAGGTCAGCTTGTGGGTTTCAATCTTTTTATTCTCCCGCCAGGGACATG
GGTGATATTGTCCAGGGACCCGATCTTCGACTGCACTCTGTCTTGAAGTCCAGCTTCTCAGATTTTACT
TCCACCTGGCCACCTCCTGGTTTATGATGGATGTTGCCTAATGAGCCACACTTGGAGGTACCTTGTCTCA
GGTCAACTGGTTTGTAGACTATTTGACACTGCCGCTCCCGGGACGTGTTTGATATTATCTTTGAGCC
50 ACACTTGGACTGGACGTTGCTAAGATCCAGCTTCTTATTAATTATCTGCACCTTCCCGCTCCCGGCTGG
TGCTTCAGGTTCTCGTGGAGCCGATCTTGGACTTACGTTCTTTCAGGTCTGGCATGGGCACGGGGGCTG
TCTGCAGGCGGCTCTTGGCGGAAGACGGCGACTTAGGTGGAGTACGGACCACCGCCACCTTCTTGGGCTC
CCGGGCTGGAGGGTTGGAAGGACGGGGTGGGGAGCGGCTGCCGGGAGTGCCCGGGGAGCCGGGGCTG
CTGTAGCCACTGCGATCCCTGATTTTGGAGGTTACACAGAGCTGGGTGGTGTCTTTGGGGCGGGCGGG
55 TTTTGTGGAAATCCTGGTGGCGTTGGCTTGGCCCTTCTGGCTGGAGGGGGCGCTCCCGGGGTGTGGC
GATCTTCGTTTTCCCATCAGCCCCCTTGGCTTTTTTGTATCGCTTCCAGTCCCGTCTTTGCTTTTACTG
ACCATGCGAGCTTGGGTACGTGACCAGCAGCTTCGTCTTCCAGGCTGGGGGTGTCTCCGATGCCTGCTT
CCTCAGCTGTGGTTCTCTTGGGATCTCCATGTGGGGCTGGGCGGCAGCCTGCTCGCCGGGAGCTCTCTC
ATCCACTAAGGGCGCTGTCACATCTTCCGCCGTTGGAGTGCTCTTAGCATCAGAGGTTTTCAGAGCCAGT
60 TCCTCAGATCCATCCTCAGCGGGGTCTGCAGGGGAGATTCTTTCAGGCCAGCGTCCGTGTACCCCTCTT
GGTCTTGGAGCATGGTGTAGCCCTTTGATCTTTCTGTCCCCAACCCGTACGTCCAGCGTGATCTTC

CATCACATCGAACTCCTGGCGGGGCTCAGCCATCCTGGTTCAAGGCTCGCCTGATAGTCGACAGAGGCGA
GGACGGGAGAGGACAGCGGAGGAGGAGAAGGTGGCTGTGGTGGCGGCGGCAGAAAGGTGGGCGGTGGCAGC
GGCGCTGCTGTTGGTGGCGGAGCTGGTGGGTGGCGGTGACTGCGAGGGCGCGCGCCGGGGAAGAGGGCGC
GTTCCCGAGGCGGCGAGGCGGCGCAGGCGCGAGCAGCGGGAGCGCGAGCCTCCCCAGGGGAGGGGGCGGG
5 CAGCCCGGCTCCGCGGAGCCTTCTCTCCGGCCACCAGTGGGCGCGCGCAGCGCCCTGCCGCTCGGC

SEQ ID NO:9
>XM_008768277.2 PREDICTED: Rattus norvegicus microtubule-associated protein
tau (Mapt), transcript variant X7, mRNA

10 ACCGCCCACCTTCTGCTGTCGCGCGGCCACAACCACCTTCCCCTCCGCTGTCTCTTCTGTCTCTCGCCT
CCTGTGCTATTATCAGGCTTTGAAGCAGCATGGCTGAACCCCGCCAGGAGTTTGACACAATGGAAGACCAG
GCCGGAGATTACACTATGCTCCAAGACCAAGAAGGAGACATGGACCATGGCTTAAAGAGTCTCCCCAC
AGCCCCAGCCGATGATGGATCAGAAGAACCAGGTCGGAGACCTCTGATGCTAAGAGCACTCCAATGCTC
15 TGAAGACGTGACTGCGCCCCCTAGTGGAAGAGAGAGCTCCCGACAAGCAGGCGACTGCCCATGCCACAG
GAGATCCCAAGGACCAACAGCTGAAGAAGCAGGCATCGGAGACACCCCGAACATGGAGGACCAAGCTG
CTGGGCATGTGACTCAAGCTCGAGTGGCCGGCGTAAGCAAAGACAGGACAGGAAATGACGAGAAGAAAGC
CAAGGGCGCCGATGGCAAAACGGGGCGCAAGATCGCCACACCTCGGGGAGCAGCCACTCCGGGCCAGAAA
GGCACATCCAATGCCACCAGGATCCCAGCCAAGACCACACCCAGCCCAAAGACTCCTCCAGGATCAGGTG
20 AACCCACAAAATCCGGAGAACGAAGCGGCTACAGCAGCCCCGGCTCGCCCGGAACCCCTGGCAGTCGCTC
CCGTACCCCATCCCTACCAACGCGCGCCACCCGAGGCCCAAAAGGTGGCAGTGGTTCCGCACTCCCCCT
AAGTCACCGTCTGCCAGTAAGAGCCGCTACAGACTGCCCCGTGTGCCATGCCAGACCTAAAGAAGCTCA
GGTCCAAGATTGGCTCCACTGAGAACCTGAAGCACCAGCCGGGAGGCGGCAAGGTGCAGATAATTAATAA
GAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGACAATATCAAACACGTCCCGGGCGGA
GGCAGTGTGCAAATAGTCTACAAGCCAGTGGACCTGAGCAAGGTGACCTCCAAGTGTGGTTCCCTTAGGGA
25 ACATCCATCACAAGCCAGGAGGTGGCCAGGTAGAAGTAAATCAGAGAAGCTGGACTTCAAGGATAGAGT
TCAGTTCGAGATTGGCTCCTTGGATAACATCACCCATGTCCCTGGAGGAGGGAATAAGAAGATTGAAACC
CACAAGCTGACCTTCAGGGAGAATGCCAAAGCCAAGACAGACCATGGAGCAGAAATCGTGTACAAGTCAC
CTGTGGTGTCTGGGGACACATCTCCACGGCACCTCAGCAACGTCTCCTCCACGGGCAGCATCGACATGGT
GGACTCTCCACAGCTTGCACGTTAGCCGATGAAGTGTCCGCTCTTTGGCCAAGCAGGGTTTGTGATCA
30 GGCCCCTGGGGCCGTCACTGATCATGGAGAGAAGAGAGAGTGAAGTGTGGAAAAAAAAAAAAAAAAAAG
AATGACCTGGCCCCCTACCCCTCTGCCCTCCCCGTGCTCCTCATAGACAGGCTGACCAGCTTGTCACTA
ACCTGCTTTTGTGGCTCGGGTTTGGCTCGGGACTTCAAAATCAGTGATGGGAAAAAGTAAATTTTCATCTT
TCCAAATTGATTTGTGGCTAGTAATAAAATATTTTTAAGGAAGGAAAAAAAAAAAAAAAAACAGTAAACCA
TGGCCAAACAAAACCCAAACATTTCTTGGCAATTGTTATTGACCCGCCCCCCCCCTCTGAGTTTATAGAG
35 GGTGAAGGAGGCTTTGGATGGAGGCTGCTTCTGGGATTGGCTGAGGGACTAGGGCAACTAATTGCCAC
AGCCCCATCTTAGGGGATCAGGGACAGCGGCAGCAATGAAAGACTTGGGACTTGGTGTGTTTGTGGAGC
CGTAGGCAGGTGATGTTAAGTTTGTGTGGGTTTGGGAGGACTGTGATAGTGAAGGCTGAGAGATGGGT
GGGCTGGGAGTCAGAGGAGAGAGGTGAGGAAGACAGGTTGGGAGAGGGGACATTGGCTCCTTGCCAAGGA
GCTTGGGAAGCACAGGTAGCCCTGGCTGCCTGCAGCAGTCTTAGCTAGCACAGATGCCTGCCTGAGAAAG
40 CACAGTGGGTACAGTGGGTGTGTGTGCCCTTCTGAAGGGCAGCCCATGGGAGAAGGGGTATTGGGCAG
AAGGAAGGTAGGCCAGAAGGTGGCACCTTGTAGATTGGTTCTCTGAAGGCTGACCTTGCCATCCCAGGGC
ACTGGCTCCCACCCTCCAGGGAGGGAGGTCTGAGCTGAGGAGCTTCCCTTTGCTCTCACAGGAAAACCT
TGTTTACTGAGTTCTGAAGTTTGGAACTACAGCATGATTTTTGGCCACCATACAGACCTTTTAGG
GCTAACCACTTCTTTGTAAGGACTTGTGCCTCTTGCGGGAACATCTGCCTGTTCTCAAGCCTGGTCTCT
45 GGCCTTCTGCAGTGTGAGGGATGGGGTGGTAATTCTGGGATGTGGGTCCCAGGCCTCCCATCCTCGCA
CAGCCACTGTATCCCCCTACCTGTCTATCATGCCACGTCTGCCATGAGAGCCAGTCACTGCCGTCCG
TACATCACGTCTCACCGTCTGAGTGCCAGCCTCCCCAAGCCCCATCCCTGGCCCCCTGGGTAGTTATGG
CCAATATCTGCTCTACACTAGGGGTTGGAGTCCAGGGAAGGCAAAGATTGGGCCCTTGGTCTCTAGTCTCT
ACGTTGACGGAATCCAACCAAGTGTGCCTCCACAAAGGAACCTTACAACCTTGTGGTTTGGTCTCATCAT
50 TTCCCATCGTGGATGGGAGTCCGTGTGTGCCTGGAGATTACCTGGACACCTCTGCTTTTTTTTTTTTAC
TTTAGCGGTTGCCTCCTAGGCCTGACTCCTTCCCATGTTGAAGTGGAGGCAGCCACGTTAGGTGTCAATG
TCCTGGCATCAGTATGAACAGTCAGTAGTCCCAGGGCAGGGCCACACTTCTCCCATCTTCTGCTTCCACC
CCAGCTTGTGATTGTAGCCTCCCAGAGCTCAGCCGCCATTAAAGTCCCCATGCACGTAATCAGCCCTTCA
TACCCCAATTTGGGGAACATAACCCCTTGATTGAAATGTTTTCCCTCCAGTCTATGGAAGCGGTGCTGCC
55 TGCCCTGTGGAGCAGCCAGCCATCTCCAGAGACGACGCCCTTCTCTCCTGTCCGACCCCTGTTGCGCT
GTAGTCGGATTCTGCTGTTTGTCTGGGTTTACCAGAGTGAATGATAGTGAAGGAAAAAGAAAAAGAA
AAAAGAAAAAGAAAAAGGACGCATGTTATCTTGAAATATTTGTCAAAGGTTGTAGCCACC
GCAGGATTTGGAGGGCTGGATATTCCTTGTCTTCTCGTGAAGTCCAGGCCGGTGCAGTGTACCTACC
CTGCTGGGACATCCCATGTTTTGAAGGGTTTCTTCTCATCTGGGACCCTGCAGACACTGGATTGTGACA
60 TTGGAGGTCTATGACATTGGCCAAGGCCTGAAGCACAGGACCGTTAGAGGCAGCAGGCTCCGACTGTCA
GGGAGAGTGTGGCTGGCCTGTTTTCTGAGTGAAGATGGTCTCTCTAATCACAACCTCAAGTCCCAC

AGCAGCCCTGGCAGACATCTAAGAACTCCTGCATCACAAGAGAAAAGGACACTAGTACCAGCAGGGAGAG
CTGTGGCCCTAGAAATTCATGACTCTCCACTACATATCCGTGGGTCCCTTTCCAAGCCTTGGCCCTCGTCA
CCAAGGGCTTGGGATGGACTGCCCCACTGATGAAAGGGACATCTTTGGAGACCCCTTGGTTTCCAAGGC
5 GTCAGCCCCCTGACCTTGCATGACCTCCTACAGCTGTAAGGATGAGGCCTTTAAAGATTAGGAACCTCAG
GCCCAGGTCGGCCACTTTGGGCTTGGGTACAGTTAGGGACGATGCGGTAGAAGGAGGTGGCCAACCTTTC
CCATATAAGAGTTCTGTGTGCCAGAGCTACCCATTGTGTAGCTCCCCACTGCTGATGGACTTTAGCTGT
CCTTAGAAGTGAAGAGTCCAACGGAGGAAAAGGAAGTGTGGTTTGTATGGTCTGTGGTCCCTTCATCATGG
TTACCTGTGTGGTTTTCTCTCGTATACCCATTTACCCATCCTGCAGTTCCCTGTCTTGAATAGGGGTGG
10 GGGTACTCTGCCATATCTCTTGTAGGGCAGTCAGCCCCAAGTCATAGTTTGGAGTGATCTGGTCAGTGC
TAATAGGCAGTTTACAAAGGAATTCTGGCTTGTACTTTCAGTGAGGACAATCCCCAAGGGCCCTGGCAC
CTGTCTCTCTTTCCATGGCTCTCCACTGCAGAGCCAATGTCTTTGGGTGGGCTAGATAGGGTGTACAAT
TTGCCTGGTTCTCCAGCTCTTAATCCACTTTATCAATAGTTCCATTTAAATTGACTTCAATGATAAGA
GTGTATCCCATTTGAGATTGCTTGTGTGTGGGTAAAGGGGGAGGAGGAACATGTTAAGATAAATTGAC
ATGGGCAAGGGGAAGTCTTGAAGTGTAGCAGTTAAACCATCTTGTAGCCCCATTCATGATGTTGACCACT
15 TGCTAGAGAGAAGAGGTGCCATAAGGCTAGAACCTAGAGGCTTGGCTGTCCACCAACAGGCAGGCTTTT
GCAAGGCAGAGGCAGCCAGCTAGGTCCCTGACTTCCCAGCCAGGTGCAGCTCTAAGAAGTCTCTTGCCT
GCTGCCTTCTTGTGGTGTCCAGAGCCACAGCCAATGCCTCCTCAAAACCCCTGGCTTCTTCTCTTAAT
CCACTGGCACATCAGCATCACCTCCGGATTGACTTCAGATCCACAGCCTACACTACTAGCAGTGGGTAAG
ACCACTTCCTTTGTCTTGTCTGTCTTCTCCAGAAAAGTGGGCATGGAGGCGGTGTTAATAACTATAGTCT
20 ATGGCTTTATAGAGCCTTCAAACCTTCTCTAGCTTCTGAAAGGGTTACTTTTGGGCAGTATGTCAGTCTC
ACCCTCCCGATGGGCTGTAGCCTGTGCAGTTGCTGTACTGGGCATGATCTCCAGTGCTTGAAGTCCCAT
GATTTCTTTGGTGATTTTGAAGGTGGGGGAGGGACATGAATCATCTTAGCTTAGCTTCTGTCTGTGAA
TGTCCATATAGTGTACTGTGTTTTAACAAACGATTACACTGACTGTTGCTGTACAAGTGAATTTGAAA
TAAAGTTATTACTCTGATTTAA

25 SEQ ID NO:10
>Reverse Complement of SEQ ID NO:9
TTTAATCAGAGTAATAACTTTA
TTTCCAAATTCACCTTGTACAGCAACAGTCAGTGTAATCGTTTTGTAAAAACACAGTACACTATATGGACA
30 TTCACAGACAGGAAGCTAAGCTAAGATGATTCATGTCCCTCCCCCACCCTCAAAATCACCAAAAGAAATC
ATGGGACTTGCAGCACTGGAGATCATGCCAGTACAGCAACTGCACAGGCTACAGCCCATCGGGAGGGT
GAGACTGCAATACTGCCAAAAGTAACCCCTTTCAGAAGCTAGAGAGAAGTTGAAGGCTCATAAAGCCAC
AGACCTATAGTTATTAACACCGCCTCCATGCCACTTTTCTGGAGAACAGACAAGGACAAAGGAAGTGGT
CTTACCCACTGCTAGTAGTGTAGGCTGTGGATCTGAAGTCAATCCGGAGGTGATGCTGATGTGCCAGTGG
35 ATTAGAAGGAAGGAAGCCAGGGTTTTGAGGAGGCATTGGCTGTGGGCTCTGGACACCACAAGAAGGCAGC
AGGCAAGAGCAGTTCTTAGAGCTGCACCTGGCTGGGAAGTCAGGGACCTAGCTGGCTGCCCTCTGCCTTGC
AAAAGCCTGGCTGTTGGTGGGACAGCCAAGCCTTAGGTTCTAGCCTTATGGCACTCTTCTCTTAGCA
AGTGGTCAACATCATGAATGGGGCTACAAGATGGTTAACTGCTACACTTCAAGACTTCCCTTGGCCAT
GTCAATTATCTTAACATGTTCTCTCTCCCCCTTTACCCACAACACAAGCAATCTCAATGGGATACAC
40 TCTTATCATTTGAAGTCAATTTAAATGGAACATTGATAAAGTGGATTAAGAGCTTGGAGGAACCAGGCAA
ATTGTACACCCTATCTAGCCCACCCAAAAGACATTGGCTCTGCAGTGGAGAGCCATGGAAGACAGGACAG
GTGCCAGGGCCCTTGGGGGATTGTCTCACTGAAGTAACAAGCCAGAATTCCTTTGTAACTGCCTATTA
GCATGACCAGATCATCAAACTATGACTTGGGGCTGACTGCCCTACAAGAGATATGGCAGATACCC
CCACCCCTATTCAAGGACAGGAACATGCAGGATGGGTAAATGGGTATACGAGAGAAAACCACAACAGGTAA
45 CCATGATGAAGGGACCACAGACCATCAAACCACACTTCTTTTCTCCGTTGGACTCTTCACTTCTAAGG
ACAGCTAAAGTCCATCAGCAGTGGGGAGCTCACATAGGGTAGCTCTGGGCACACAGAATCTTATATGG
GAAAGGTTGGCCACCTCCTTCTACCGCATCGTCCCTAACTGTACCCAAGCCCAAAGTGGCCGACCTGGGC
CTGAGGTTCTTAATCTTTAAAGGCCTCATCCTTACAGCTGTAGGAGGTGATGCAAGGTCAGGGGGCTGAC
GCCTTGGAAACCAAGGGGTCTCCAAAGATGTCCCTTTCATCAGTGGGGCAGTCCATCCCAAGCCCTTGG
50 TGACGAGGCCAAGGCTTGGAAAGGACCCACGGATATGTAGTGGAGAGTCATGGAATTTCTAGGGCCACAG
CTCTCCCTGTGTGTACTAGTGTCTTTTCTCTTGTGATGCAGGAGTTCTTAGATGTCTGCCAGGGCTGCT
GTGGGACTTGAAGTTGTGATTAGAGAGGACCATCTTCACTCAGAGAAAACAGGCCAGCCACAAGCTCTCCC
TGACAGTCGGAGCCTGCTGCCTCTAACGGGTCTGTGCTTACAGCCTTGGCCAATGTCATAGACCTCCAA
TGTCACAATCCAGTGTCTGCAGGGTCCCAGATGAAGAAGAAACCCTTCAAAACATGGGATGTCCCAGCAG
GGTAGCACTGCACCGGCCTGGACCTAAGTCACGAAGAAGACAAGGAATATCCAGGCCCTCCAATCCCTGC
55 GGTGGGCTACAACCTTTTGACAAATATTTCAAGATAACATGCGTCTTTTTTTTTTTCTTTTTTCTTTT
TTCTTTTTTCTTTTTTCTTTTCACTATCATAGTCACTCTGGTGAACCCAGACAAAACAGACGAATCCGACTAC
AGCGCAACAGGGTGGGACAGGAGAGAAAAGGGTGGCTCTCTGGAGATGGCTGGCTGCTCCAGCAGGGCA
GGCAGCACCGCTTCCATAGGACTGGAGGGAAAACATTTCAATCAAGGGGTATGTTCCCAAAATTGGGGTA
60 TGAAGGCTGATTACGTGCATGGGACTTAATGGCGGCTGAGCTCTGGGAGGCTAGCAATCACAAGCTGG
GGTGAAGCAGAAGATGGGAGAAGTGTGGCCCTGCCCTGGGACTACTGACTGTTCATACTGATGCCAGGA

CATTGACACCTAACGTGGCTGCCTCCAGTTCAACATGGGAAGGAGTCAGGCCTAGGAGGCAACCGCTAAAGTAA
GTAAAAAAAAAAGCAGAGGTGTCCAGGGTAATCTCCAGGCACACACGGACTCCCATCCACGATGGGAA
ATGATGGAGCAAACCAAAGGTTGTAAGGTTCTTGTGGGAGGCACACTGGTTGGATTCTGCAACGT
AGGACTAGAGACCAAGGCCAAATCTTGCCTTCCCTGGACTCCAACCCCTAGTGTAGAGCAGATATTGG
5 CCATAACTACCCAGGGGCCAGGGATGGGGCTTGGGGAGGCTGGGCACTCAGGACGGTGAGACGTGATGTA
CGGACGGCAGTGAAGTGTCTCATGGCAGACGTGGGCATGATAGGACAGGTAGAGGGGATACAGTGGCTG
TGCGAGGATGGGAGGCTGGGACCCACATCCCAGAATTACCACCCCATCCCTCACACTGCAGAAGTGCC
AGAGGACCAGGCTTGAGAACAGGCAGATGTTCCCGCAAGAGGCACAAGTCCTTACAAAGAACTGGTTAGC
10 CCTAAAGTCCCAGGTCTGTATGGTGGCCAAAATCATGGCTGTAGTTCCAAACTTCAGAACTCAGTAACAC
AGGTTTTCTGTGAGAGCAAAGGGAAGCTCCTCAGCTCAGGACCTCCCTCCCTGGAGGGTGGGAGCCAGT
GCCCTGGGATGGCAAGGTCAGCCTTCAGAGAACCAATCTACAAGGTGCCACCTTCTGGCTACCTTCTCTT
CTGCCCCAATACCCCTTCTCCCATGGGCTGCCCTTCAGAAGGGGCACACACACCCACTGTACCCCACTGTG
CTTTCTCAGGCAGGCATCTGTGCTAGCTAAGACTGCTGCAGGCAGCCAGGGCTACCTGTGCTTCCCAAGC
TCCCTTGGCAAGGAGCCAATGTCCCTCTCCCAACCTGTCTTCTCACCTCTCTCTCTGACTCCCAGCCC
15 ACCCATCTCTCAGCCTTCACTATCACAGTCTCTCCCTCAAACCCACACAAAGTTAATCATCTGCCTACG
GCTCCACAAACACACCAAGTCCCAAGTCTTTTATTGCTGCCGCTGTCCCTGATGCCCCTAAGATGGGGCT
GTGGGCAATTAGTTGCCCTAGTCCCTCAGCCAATCCCCAGAAGCAGCCTCCATCCAAAGCCTCCTTCACC
CTCTAAAACTCAGAGGGGGGGGGCGGGTCAATAACAATTGCCAAGGAAATGTTGGGTTTTGTTGGCCA
TGGTTTTACGTGTTTTTTTTTTTTTCTTCTTAAAAATATTTTATTACTAGCCACAAATCAATTTGGA
20 AAGATGAATTTTACTTTTTTCCCATCACTGATTTTTGAAGTCCCGAGCCAAACCCGAGCCACAAAAGCAGGT
TAGGTGACAAGCTGGTCAGCCTGTCTATGAGGAGCAGCGGGAGGGCAGAGGGTGAGGGGCCAGGTCATT
CTTTTTTTTTTTTTTTTTTCCACACTCTCACTCTCTTCTCTCCATGATCAGTGACGGCCCCAGGGGCC
TGATCACAAACCCTGCTTGGCCAAAGAGGCGGACACTTCATCGGCTAACGTGGCAAGCTGTGGAGAGTCC
ACCATGTCGATGCTGCCGTGGAGGAGACGTTGCTGAGGTGCCGTGGAGATGTGTCCCCAGACACCACAG
25 TGACTTTGTACAGATTCTGCTCCATGGTCTGTCTTGGCTTTGGCATTCTCCCTGAAGGTCAGCTTGTG
GGTTTTCAATCTTCTTATTCCTCCTCCAGGGACATGGGTGATGTTATCCAAGGAGCCAATCTTCGACTGG
ACTCTATCCTTGAAGTCCAGCTTCTCTGATTTTACTTCTACCTGGCCACCTCCTGGCTTGTGATGGATGT
TCCCTAAGGAACCACACTTGGAGGTACCTTGGCTCAGGTCCACTGGCTTGTAGACTATTTGCACACTGCC
TCCGCCCGGGACGTGTTTGATATTGCTCTTGGCCACACTTGGACTGGACGTGCTAAGATCCAGCTTC
30 TTATTAATTATCTGCACCTTGGCCCTCCCGGCTGGTGTCTCAGGTTCTCAGTGGAGCCAATCTTGGACC
TGACGTTCTTTAGGTCTGGCATGGGCACAGGGGAGTCTGTAGGCGGCTCTTACTGGCAGACGGTCACTT
AGGGGGAGTGCGAACCACTGCCACCTTTTTGGGCTCTCGGGTGGGCGCGTGGTAGGGATGGGGTACGG
GAGCGACTGCCAGGGGTTCGGGGCAGCCGGGGCTGCTGTAGCCGCTTCGTTCTCCGGATTTTGGTGGTT
CACCTGATCCTGGAGGAGTCTTTGGGCTGGGTGTGGTCTTGGCTGGGATCCTGGTGGCATTGGATGTGCC
35 TTTCTGGCCCGGAGTGGCTGCTCCCCGAGGTGTGGCGATCTTCGCCCCGTTTTGCCATCGGCGCCCTTG
GCTTTCTTCTCGTCATTTCCTGTCTGTCTTTGCTTACGCCGGCCACTCGAGCTTGAGTCACATGCCACG
CAGCTTGGTCTCCTCCTGTTTCGGGGTGTCTCCGATGCTTCTTTCAGCTGTGGTGCCTTCTGGGATCTC
CGTGTGGGACTGGGCAGTGCCTGCTTGTGGGAGCTCTCTCTTCCACTAGGGGCGCAGTCACGTCTTCA
GCAGTTGGAGTGTCTTTAGCATCAGAGGTCTCCGACCCTGGTTCTTCTGATCCATCATCGGCTGGGGGCT
40 GTGGGGGAGACTCTTTTAAGCCATGTTCCATGTCTCCTTCTTGGTCTTGGAGCATAGTGTAACTCTCCGGC
CTGGTCTTCCATTGTGTCAAACCTCTGGCGGGGTTAGCCATGCTGCTTCAAAGCCTGATAATCGACAGG
AGGCGAGGACAGAAGAGGACAGCGGAGGGGAAGGTGGTTGTGGCGGCGGCACAGCAGAAGGTGGGCGGT

SEQ ID NO:11

45 >XM_005624183.3 PREDICTED: Canis lupus familiaris microtubule associated
protein tau (MAPT), transcript variant X23, mRNA
CGCGCTCGCGCTCTCAGCCACCCACCAGCTCCCGCACCAGCAGCAGCAGCGCGCGCGCGCGCGCGCGC
CGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGC
TGTCGACTATCAGGTGGGCGCTTGACCTAGGATGGCTGAGCCCCGCCAGGAGTTCAGTGTGATGGAAGATC
50 ATGCTGGGACATACGGGAAAGATCTCCCTCTCAGGGGGGCTACACCCTGTGCAAGACCATGAGGGGGA
CGTGGATCAGGGCTGAAAGCTGAAGAAGCAGGCATTGGAGACACCCCAACCTGGAAGACCAAGCTGCT
GGACATGTGACTCAAGCTCGCATGGTCAGTAAAGGCAAGATGGGACTGGAACCGATGACAAAAAGCCA
AGGGGGCTGATGGTAAACTGGAACGAAGATCGCCACACCCCGGGGAGCGACCCCTTCAGGCCAGAAAGG
CCAGGCCAATGCCACCAGGATTCCAGCGAAAACACGCGCTCCCCAAGACCCACCGGGCGGTGAATCT
55 GGAAAAATCTGGGGATCGCAGTGGCTACAGCAGCCCCGGCTCCCCAGGCACTCCTGGCAGCGCTCCCCGA
CCCCGTCCCTGCCAACCCACCCACCCGGGAGCCCAAGAAGGTGGCGGTGGTCCGCACCCACCCCAAGTC
GCCGTCTGCAGCCAAGAGTCGCCTGCAGACCGCCCTGTGCCATGCCAGACCTAAAGAAGCTCAGATCC
AAGATCGGCTCCACTGAAAACCTGAAGCACCAGCCAGGAGGTGGGAAGGTGCAAAATAGTGTACAAACCAG
TGGATCTGAGCAAGGTGACCTCCAAGTGCAGGCTCATTAGGCAACATCCATCATAAGCCAGGAGGCGGTCA
60 GGTGGAAGTCAAATCTGAGAAGCTGGAATTCAGGACAGAGTCCAGTCAAGATCGGGTCCCTGGACAAC
ATCACCCACGTCCCTGGCGGAGGGAATAAAAAGATCGAAACCCACAAGCTGACCTTCCGTGAGAACGCCA

5 AAGCCAAGACCGACCACGGGGCGGAGATCGTGTACAAGTCGCCCGTGGTGTCCGGGGACACGTCTCCGCG
GCACCTGAGCAACGTGTCCCTCCACGGGCAGCATCGACATGGTTCGACTCGCCCCAGCTCGCCACGCTAGCC
GACGAAGTGTCCGCCTCCCTGGCCAAGCAGGGTTTGTGATCAGGCCCCGGGGCGGTCAATGATCGTGGA
GAGAAGAGAGTGTGGAAAAAAAAAAGAATAATGATCTGGCCCTTCTCGCCCTCTGCCCTCCCCAGCTGCT
10 CCTCACAGACCGGTTAATCGGTAAATCACTTAACCTGCTTTTGTGCTCGGCTCTGGCTCGGGACTTCAA
AATCAGTGACGGGAAAAAGCAAATTTTCATCTTTCCAAATTGATGGGTGGGCTAATAATAAAAAATATTT
TTAAAACCATTTAAAAA

SEQ ID NO:12
10 >Reverse Complement of SEQ ID NO:11
TTTTTAAATGGTTTTAA
AAATATTTTATTATTATTAGCCCACCCATCAATTTGGAAAGATGAAATTTGCTTTTTCCCGTCACTGATT
TTGAAGTCCCGAGCCAGAGCCGAGCGACAAAAGCAGGTAAAGTGATTAACCGATTAACCGGTCTGTGAGG
AGCAGCTGGGGGAGGGCAGAGGGCGAGAAGGGCCAGATCATTATTCCTTTTTTTTTTCCACACTCTCTTCTC
15 TCCACGATCATTGACCGCCCCGGGGCGCTGATCACAAACCCTGCTTGCCAGGGAGGCGGACACTTCGTC
GGCTAGCGTGGCGAGCTGGGGCGAGTCGACCATGTGATGCTGCCCGTGGAGGACACGTTGCTCAGGTGC
CGCGGAGACGTGTCCCGGACACCACGGGCGACTTGTACACGATCTCCGCCCGTGGTGGTCTTGGCTT
TGGCGTTCTCACGGAAGGTCAGCTTGTGGGTTTCGATCTTTTTATTCCCTCCGCCAGGGACGTGGGTGAT
GTTGTCCAGGGACCCGATCTTCGACTGGACTCTGCTCTTGAAGTCCAGCTTCTCAGATTTGACTTCCACC
20 TGACCGCCTCCTGGCTTATGATGGATGTTGCCTAATGAGCCGCACTTGGAGGTCACCTTGCTCAGATCCA
CTGGTTTGTACACTATTTGCACCTTCCCACCTCCTGGCTGGTGTTCAGGTTTTCAGTGGAGCCGATCTT
GGATCTGACGTTCTTTAGGTCTGGCATGGGCACAGGGGCGGTCTGCAGGCGACTCTTGGCTGCAGACGGC
GACTTGGGTGGGGTGCAGACACCGCCACCTTCTTGGGCTCCCGGGTGGGTGGGGTTGGCAGGGACGGGG
TGCGGGAGCGGCTGCCAGGAGTGCTGGGGAGCCGGGGCTGCTGTAGCCACTGCGATCCCCAGATTTTCC
25 AGATTACCGCCCGGTGGGGTCTTGGGGGAGGGCTGGTTTTTCGCTGGAATCCTGGTGGCATTGGCCTGG
CCTTTCTGGCCTGAAGGGTCTGCTCCCGGGGTGTGGCGATCTTCGTTCCAGTTTTACCATCAGCCCCCT
TGGCTTTTTTGTATCGGTTCCAGTCCCATCTTTGCCTTTACTGACCATGCGAGCTTGAGTCACATGTCC
AGCAGCTTGGTCTTCCAGGTGGGGTGTCTCCAATGCCTGCTTCTTCAGCTTTCAGGCCGTGATCCACG
TCCCCCTCATGGTCTTGCAGCAGGGTGTAGCCCCCTGAGAGGGGAGATCTTCCCGTATGTCCAGCAT
30 GATCTTCCATCACAGTGAACCTCCTGGCGGGGCTCAGCCATCCTAGGTCAAGGCCACCTGATAGTCGACA
GAGGGCGAGGACAGGAGAGGAAAGAGAGAAAGTGGCTGTGGTGGCGGCAGCAGAAGGTGGGCGGCGGCG
GCGGCGGCGGCGGCGGCGGCTGCTGCTGCTGGTGGGAGGCTGGTGGGTGGCTGAGAGCGCGAGCGCG

SEQ ID NO:1533
35 >MAPT (NM_005910) exon 10
GTGCAAATAGTCTACAAACAGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTA
GGCAACATCCATCATAAACAG

CLAIMS

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence selected from a group consisting of SEQ ID NO: 1 and SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence selected from a group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence selected from a group consisting of SEQ ID NO:2 and SEQ ID NO: 4.

3. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 3-8 and 16-28.

4. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 512-532, 513-533, 514-534, 515-535, 516-536, 517-537, 518-538, 519-539, 520-540, 1063-1083, 1067-1087, 1072-1092, 1074-1094, 1075-1095, 1125-1145, 1126-1146, 1127-1147, 1129-1149, 1170-1190, 1395-1415, 1905-1925, 1906-1926, 1909-1929, 1911-1931, 1912-1932, 1913-1933, 1914-1934, 1915-1935, 1916-1936, 1919-1939, 1951-1971, 1954-1974, 1958-1978, 2387-2407, 2409-2429, 2410-2430, 2469-2489, 2471-2491, 2472-2492, 2476-2496, 2477-2497, 2478-2498, 2480-2500, 2481-2501, 2482-2502, 2484-2504, 2762-2782, 2764-2784, 2766-2786, 2767-2787, 2768-2788, 2769-2789, 2819-2839, 2821-2841, 2828-2848, 2943-2963, 2944-2964, 2946-2966, 2947-2967, 3252-3272, 3277-3297, 3280-3300, 3281-3301, 3282-3302, 3284-3304, 3285-3305, 3286-3306, 3331-

3351, 3332-3352, 3333-3353, 3334-3354, 3335-3355, 3336-3356, 3338-3358, 3340-3360, 3342-3362, 3343-3363, 3344-3364, 3345-3365, 3346-3366, 3347-3367, 3349-3369, 3350-3370, 3353-3373, 3364-3384, 3366-3386, 3367-3387, 3368-3388, 3369-3389, 3370-3390, 3412-3432, 3414-3434, 3415-3435, 3416-3436, 3417-3437, 3419-3439, 3420-3440, 3424-3444, 3425-3445, 3426-3446, 3427-3447, 3428-3448, 3429-3449, 3430-3450, 3431-3451, 3434-3454, 4132-4152, 4134-4154, 4179-4199, 4182-4202, 4184-4204, 4395-4415, 4425-4445, 4426-4446, 4429-4449, 4469-4489, 4470-4490, 4471-4491, 4472-4492, 4473-4493, 4474-4494, 4569-4589, 4571-4591, 4572-4592, 4596-4616, 4623-4643, 4721-4741, 4722-4742, 4725-4745, 4726-4746, 4766-4786, 4767-4787, 4768-4788, 4769-4789, 4770-4790, 4779-4799, 4805-4825, 4806-4826, 4807-4827, 4808-4828, 4809-4829, 4812-4832, 4813-4833, 4814-4834, 4936-4956, 5072-5092, 5073-5093, 5345-5365, 5346-5366, 5349-5369, 5350-5370, 5351-5371, 5460-5480, 5461-5481, 5463-5483, 5465-5485, 5467-5487, 5468-5488, 5469-5489, 5470-5490, 5471-5491, 5505-5525, 5506-5526, 5507-5527, 5508-5528, 5509-5529, 5511-5531, 5513-5533, 5514-5534, 5541-5561, 5544-5564, 5546-5566, 5547-5567, 5548-5568, 5550-5570, 5551-5571, 5574-5594, 5576-5596, 5614-5634, 521-541, 522-542, 523-543, 524-544, 525-545, 526-546, 527-547, 528-548, 529-549, 530-550, 531-551, 532-552, 533-553, 534-554, 535-555, 536-556, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063, 1044-1064, 1045-1065, 1046-1066, 1047-1067, 1048-1068, 1049-1069, 1050-1070, 1051-1071, 1052-1072, 1053-1073, 1054-1074, 1062-1082, 1064-1084, 1065-1085, 1066-1086, 1068-1088, 1069-1089, 1070-1090, 1071-1091, 1073-1093, 1076-1096, 1077-1097, 1078-1098, 1079-1099, 1080-1100, 1081-1101, 1082-1102, 1128-1148, 1129-1149, 1130-1150, 1131-1151, 1132-1152, 1133-1153, 1134-1154, 1135-1155, 1136-1156, 1137-1157, 1138-1158, 1139-1159, 1140-1160, 1141-1161, 1142-1162, 1143-1163, 1144-1164, 1145-1165, 1146-1166, 1147-1167, 1148-1168, 975-995, 976-996, 977-997, 978-998, 979-999, 980-1000, 981-1001, 982-1002, 983-1003, 984-1004, 985-1005, 986-1006, 987-1007, 988-1008, 989-1009, 990-1010, 991-1011, 992-1012, 993-1013, 994-1014, 995-1015, 996-1016, 997-1017, 998-1018, 999-1019, 1000-1020, 1001-1021, 1002-1022, 1003-1023, 1004-1024, 1005-1025, 1006-1026, 1007-1027, 1008-1028, 1009-1029, 1010-1030, 1011-1031, 1012-1032, 1013-1033, 1014-1034, 1015-1035, 1016-1036, 1017-1037, 1018-1038, 1019-1039, 1020-1040, 1021-1041, 1022-1042, 1023-1043, 1024-1044, 1025-1045, 1026-1046, 1027-1047, 1028-1048, 1029-1049, 1030-1050, 1031-1051, 1032-1052, 1033-1053, 1034-1054, 1035-1055, 1036-1056, 1037-1057, 1038-1058, 1039-1059, 1040-1060, 1041-1061, 1042-1062, 1043-1063 and 1045-1065 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

5. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 520-541, 520-556, 510-534, 512-536, 516-541, 516-540, 520-544, 524-547, 526-551, 529-556, 532-556, 1065-1089, 1068-1095, 1068-1094, 1075-1100, 1076-1100, 1079-1103, 1123-1147, 1127-1151, 1130-1155, 1903-1934, 1903-1930, 1914-1940, 1949-1975, 2470-2497, 2941-2965, 3275-3302, 3278-3302, 3329-3353, 3333-3357, 3338-3367, 3338-3366, 3348-3390, 3348-3388,

3351-3385, 5507-5562 and 5549-5597 of SEQ ID NO: 3, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 4.

6. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 977-997, 980-1000, 973-993, 988-1008, 987-1007, 972-992, 979-999, 1001-1021, 976-996, 994-1014, 1002-1022, 978-998, 974-994, 520-540, 521-541, 5464-5484, 1813-1833, 2378-2398, 3242-3262, 5442-5462, 1665-1685, 524-544, 5207-5227, 4670-4690, 3420-3440, 3328-3348, 5409-5429, 5439-5459, 4527-4547, 5441-5461, 5410-5430 and 5446-5466 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

7. The dsRNA agent of any one of claims 1-6, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-523799.1, AD-523802.1, AD-523795.1, AD-523810.1, AD-523809.1, AD-1019331.1, AD-523801.1, AD-523823.1, AD-523798.1, AD-523816.1, AD-523824.1, AD-523800.1, AD-523796.1, AD-535094.1, AD-535094.1, AD-535095.1, AD-538647.1, AD-535922.1, AD-536317.1, AD-536911.1, AD-538626.1, AD-535864.1, AD-523561.1, AD-523565.1, AD-523562.1, AD-526914.1, AD-526394.1, AD-395452.1, AD-525343.1, AD-524274.1, AD-526956.1, AD-526986.1, AD-526296.1, AD-526988.1, AD-526957.1, AD-526993.1, AD-1397070.1, AD-1397070.2, AD-1397071.1, AD-1397071.2, AD-1397072.1, AD-1397072.2, AD-1397073.1, AD-1397073.2, AD-1397074.1, AD-1397074.2, AD-1397075.1, AD-1397075.2, AD-1397076.1, AD-1397076.2, AD-1397077.1, AD-1397077.2, AD-1397078.1, AD-1397078.2, AD-1397250.1, AD-1397251.1, AD-1397252.1, AD-1397253.1, AD-1397254.1, AD-1397255.1, AD-1397256.1, AD-1397257.1, AD-1397258.1, AD-1397259.1, AD-1397260.1, AD-1397261.1, AD-1397262.1, AD-1397263.1, AD-1397264.1, AD-1397265.1, AD-1423242.1, AD-1423243.1, AD-1423244.1, AD-1423245.1, AD-1423246.1, AD-1423247.1, AD-1423248.1, AD-1423249.1, AD-1423250.1, AD-1423251.1, AD-1423252.1, AD-1423253.1, AD-1423254.1, AD-1423255.1, AD-1423256.1, AD-1423257.1, AD-1423258.1, AD-1423259.1, AD-1423260.1, AD-1423261.1, AD-1423262.1, AD-1423263.1, AD-1423264.1, AD-1423265.1, AD-1423266.1, AD-1423267.1, AD-1423268.1, AD-1423269.1, AD-1423270.1, AD-1423271.1, AD-1423272.1, AD-1423273.1, AD-1423274.1, AD-1423275.1, AD-1423276.1, AD-1423277.1, AD-1423278.1, AD-1423279.1, AD-1423280.1, AD-1423281.1, AD-1423282.1, AD-1423283.1, AD-1423284.1, AD-1423285.1, AD-1423286.1, AD-1423287.1, AD-1423288.1, AD-1423289.1, AD-1423290.1, AD-1423291.1, AD-1423292.1, AD-1423293.1, AD-1423294.1, AD-1423295.1, AD-1423296.1, AD-1423297.1, AD-1423298.1, AD-1423299.1, AD-1423300.1, AD-1397266.1, AD-1397266.2, AD-1397267.1, AD-1423301.1, AD-1397268.1, AD-1397268.2, AD-1397269.1, AD-1423302.1, AD-1397270.1, AD-1397270.2, AD-1397271.1, AD-1397271.2, AD-1397272.1, AD-

1423303.1, AD-1397273.1, AD-1423304.1, AD-1397274.1, AD-1423305.1, AD-1397275.1, AD-1423306.1, AD-1397276.1, AD-1397277.1, AD-1397277.2, AD-1397278.1, AD-1397279.1, AD-1397280.1, AD-1397281.1, AD-1397282.1, AD-1397283.1, AD-1397284.1, AD-1397285.1, AD-1397286.1, AD-1397287.1, AD-1397079.1, AD-1397079.2, AD-1397288.1, AD-1397289.1, AD-1397290.1, AD-1397080.1, AD-1397080.2, AD-1397291.1, AD-1397292.1, AD-1397293.1, AD-1397294.1, AD-1397081.1, AD-1397081.2, AD-1397295.1, AD-1397082.1, AD-1397082.2, AD-1397083.1, AD-1397083.2, AD-1397296.1, AD-1397297.1, AD-1397298.1, AD-1397299.1, AD-1397300.1, AD-1397301.1, AD-1397302.1, AD-1397084.1, AD-1397085.1, AD-1397086.1, AD-1397303.1, AD-1397087.1, AD-1397087.2, AD-1397304.1, AD-1397305.1, AD-1397306.1, AD-1397307.1, AD-1397308.1, AD-1397309.1, AD-1397310.1, AD-1397311.1, AD-1397312.1, AD-1397313.1, AD-1397314.1, AD-1397315.1, AD-1397316.1, AD-1397317.1, AD-1397318.1, AD-1397319.1, AD-1397320.1, AD-1397321.1, AD-1397322.1, AD-1397088.1, AD-1397089.1, AD-1397090.1, AD-1397091.1, AD-1397092.1, AD-1397093.1, AD-1397094.1, AD-1397095.1, AD-1397096.1, AD-1397097.1, AD-1397098.1, AD-1397099.1, AD-1397101.1, AD-1397102.1, AD-1397103.1, AD-1397104.1, AD-1397105.1, AD-1397106.1, AD-1397107.1, AD-1397108.1, AD-1397109.1, AD-1397110.1, AD-1397111.1, AD-1397112.1, AD-1397113.1, AD-1397114.1, AD-1397115.1, AD-1397116.1, AD-1397117.1, AD-1397118.1, AD-1397119.1, AD-1397120.1, AD-1397121.1, AD-1397122.1, AD-1397123.1, AD-1397124.1, AD-1397125.1, AD-1397126.1, AD-1397127.1, AD-1397128.1, AD-1397129.1, AD-1397130.1, AD-1397131.1, AD-1397132.1, AD-1397133.1, AD-1397134.1, AD-1397135.1, AD-1397136.1, AD-1397137.1, AD-1397138.1, AD-1397139.1, AD-1397140.1, AD-1397141.1, AD-1397142.1, AD-1397143.1, AD-1397144.1, AD-1397145.1, AD-1397146.1, AD-1397147.1, AD-1397148.1, AD-1397149.1, AD-1397150.1, AD-1397151.1, AD-1397152.1, AD-1397153.1, AD-1397154.1, AD-1397155.1, AD-1397156.1, AD-1397157.1, AD-1397158.1, AD-1397159.1, AD-1397160.1, AD-1397161.1, AD-1397162.1, AD-1397163.1, AD-1397164.1, AD-1397165.1, AD-1397166.1, AD-1397167.1, AD-1397168.1, AD-1397169.1, AD-1397170.1, AD-1397171.1, AD-1397172.1, AD-1397173.1, AD-1397174.1, AD-1397175.1, AD-1397176.1, AD-1397177.1, AD-1397178.1, AD-1397179.1, AD-1397180.1, AD-1397181.1, AD-1397182.1, AD-1397183.1, AD-1397184.1, AD-1397185.1, AD-1397186.1, AD-1397187.1, AD-1397188.1, AD-1397189.1, AD-1397190.1, AD-1397191.1, AD-1397192.1, AD-1397193.1, AD-1397194.1, AD-1397195.1, AD-1397196.1, AD-1397197.1, AD-1397198.1, AD-1397199.1, AD-1397200.1, AD-1397201.1, AD-1397202.1, AD-1397203.1, AD-1397204.1, AD-1397205.1, AD-1397206.1, AD-1397207.1, AD-1397208.1, AD-1397209.1, AD-1397210.1, AD-1397211.1, AD-1397212.1, AD-1397213.1, AD-1397214.1, AD-1397215.1, AD-1397216.1, AD-1397217.1, AD-1397218.1, AD-1397219.1, AD-1397220.1, AD-1397221.1, AD-1397222.1, AD-1397223.1, AD-1397224.1, AD-1397225.1, AD-1397226.1, AD-1397227.1, AD-1397228.1, AD-1397229.1, AD-1397230.1, AD-1397231.1, AD-1397232.1, AD-1397233.1, AD-1397234.1, AD-1397235.1, AD-1397236.1, AD-1397237.1, AD-1397238.1, AD-1397239.1, AD-1397240.1, AD-1397241.1, AD-1397242.1, AD-1397243.1, AD-1397244.1, AD-1397245.1, AD-1397246.1, AD-

1397247.1, AD-1397248.1, AD-1397249.1, AD-523565.1, AD-1397072.3, AD-1397073.3, AD-1397076.3, AD-1397077.3, AD-1397078.3, AD-1397252.2, AD-1397257.2, AD-1397258.2, AD-1397259.2, AD-1397263.2, AD-1397264.2, AD-1397309.2, AD-64958.114, AD-393758.4, AD-1397080.3, AD-1397293.2, AD-1397294.2, AD-1397081.3, AD-1397083.3, AD-1397298.2, AD-1397299.2, AD-1397084.2, AD-1397085.2, AD-1397087.3, AD-1397306.2, AD-1397307.2, AD-1397308.2, AD-1397088.2, AD-1566238, AD-1566239, AD-1566240, AD-1566241, AD-1566242, AD-1566243, AD-1566244, AD-1566245, AD-1566246, AD-1091965, AD-1566248, AD-1566249, AD-1566250, AD-1091966, AD-1566251, AD-1566252, AD-1566253, AD-1566254, AD-1566255, AD-1566256, AD-1566257, AD-1566258, AD-1566259, AD-692906, AD-1566575, AD-1566576, AD-1566577, AD-1566580, AD-1566581, AD-1566582, AD-1566583, AD-1566584, AD-1566586, AD-1566587, AD-1566588, AD-1566590, AD-1566591, AD-1566634, AD-1566635, AD-1566638, AD-1566639, AD-1566641, AD-1566642, AD-1566643, AD-1566679, AD-1566861, AD-1567153, AD-1567154, AD-1567157, AD-1567159, AD-1567160, AD-1567161, AD-1567164, AD-1567167, AD-1567199, AD-1567202, AD-1567550, AD-1567554, AD-1567784, AD-1567896, AD-1567897, AD-1568105, AD-1568108, AD-1568109, AD-1568139, AD-1568140, AD-1568143, AD-1568144, AD-1568148, AD-1568150, AD-1568151, AD-1568152, AD-1568153, AD-1568154, AD-1568158, AD-1568161, AD-1568172, AD-1568174, AD-1568175, AD-692908, AD-1568176, AD-1569830, AD-1569832, AD-1569834, AD-1569835, AD-1569862, AD-1569872, AD-1569890 and AD-1569892.

8. The dsRNA agent of claim 1 or 2, wherein the nucleotide sequence of the sense and antisense strand comprise any one of the sense and antisense strand nucleotide sequences in any one of Tables 3-8 and 16-28.

9. The dsRNA agent of claim 1 or 2, wherein the nucleotide sequence of the sense strand comprises at least 15 contiguous nucleotides corresponding to the MAPT gene exon 10 sense strand sequence set forth in SEQ ID No.: 1533 and an antisense strand comprising a sequence complementary thereto.

10. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 5 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 6.

11. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:6.

12. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding Tau, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 12-13.

13. The dsRNA agent of any one of claims 10-12, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 1065-1085, 1195-1215, 1066-1086, 1068-1088, 705-725, 1067-1087, 4520-4540, 3341-3361, 4515-4535, 5284-5304, 5285-5305, 344-364, 5283-5303, 5354-5374, 2459-2479, 1061-1081, 706-726, 972-992, 4564-4584, 995-1015, 4546-4566, 968-988, 1127-1147, 4534-4554, 158-178, 4494-4514, 1691-1711, 3544-3564, 198-218, 979-999, 4548-4568, 4551-4571, 543-563, 715-735, 542-562, 352-372, 362-382, 4556-4576, 4547-4567, 4542-4562, 4558-4578, 4549-4569, 5074-5094, 4552-4572, 5073-5093, 5076-5096, 4550-4570 and 2753-2773 of SEQ ID NO: 5, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 6.

14. The dsRNA agent of any one of claims 10-13, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-393758.1, AD-393888.1, AD-393759.1, AD-393761.1, AD-393495.1, AD-393760.1, AD-396425.1, AD-395441.1, AD-396420.1, AD-397103.1, AD-397104.1, AD-393239.1, AD-397102.1, AD-397167.1, AD-394791.1, AD-393754.1, AD-393496.1, AD-393667.1, AD-396467.1, AD-393690.1, AD-396449.1, AD-393663.1, AD-393820.1, AD-396437.1, AD-393084.1, AD-396401.1, AD-394296.1, AD-395574.1, AD-393124.1, AD-393674.1, AD-396451.1, AD-396454.1, AD-393376.1, AD-393505.1, AD-393375.1, AD-393247.1, AD-393257.1, AD-396459.1, AD-396450.1, AD-396445.1, AD-396461.1, AD-396452.1, AD-396913.1, AD-396455.1, AD-396912.1, AD-396915.1, AD-396453.1 and AD-394991.1.

15. The dsRNA agent of any one of claims 1-14, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.
16. The dsRNA agent of claim 15, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.
17. The dsRNA agent of claim 15 or 16, wherein the lipophilic moiety is conjugated via a linker or carrier.
18. The dsRNA agent of any one of claims 15-17, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.
19. The dsRNA agent of any one of claims 1-18, wherein the hydrophobicity of the double-stranded RNA agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNA agent, exceeds 0.2.
20. The dsRNA agent of claim 19, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.
21. The dsRNA agent of any one of claims 1-20, wherein the dsRNA agent comprises at least one modified nucleotide.
22. The dsRNA agent of claim 21, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.
23. The dsRNA agent of claim 21, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.
24. The dsRNA agent of any one of claims 21-23, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a

1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofuran-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

25. The dsRNA agent of claim 24, wherein the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxythymidine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

26. The dsRNA agent of claim 24, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxythymidine nucleotides (dT).

27. The dsRNA agent of claim 24, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2' fluoro modifications.

28. The dsRNA agent of any one of claims 1-27, further comprising at least one phosphorothioate internucleotide linkage.

29. The dsRNA agent of claim 28, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

30. The dsRNA agent of any one of claims 1-29, wherein each strand is no more than 30 nucleotides in length.

31. The dsRNA agent of any one of claims 1-30, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

32. The dsRNA agent of any one of claims 1-31, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

33. The dsRNA agent of any one of claims 1-32, wherein the double stranded region is 15-30 nucleotide pairs in length.
34. The dsRNA agent of claim 33, wherein the double stranded region is 17-23 nucleotide pairs in length.
35. The dsRNA agent of claim 33, wherein the double stranded region is 17-25 nucleotide pairs in length.
36. The dsRNA agent of claim 33, wherein the double stranded region is 23-27 nucleotide pairs in length.
37. The dsRNA agent of claim 33, wherein the double stranded region is 19-21 nucleotide pairs in length.
38. The dsRNA agent of claim 33, wherein the double stranded region is 21-23 nucleotide pairs in length.
39. The dsRNA agent of any one of claims 1-38, wherein each strand has 19-30 nucleotides.
40. The dsRNA agent of any one of claims 1-37, wherein each strand has 19-23 nucleotides.
41. The dsRNA agent of any one of claims 1-38, wherein each strand has 21-23 nucleotides.
42. The dsRNA agent of any one of claims 16-41, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.
43. The dsRNA agent of claim 42, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.
44. The dsRNA agent of claim 43, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.
45. The dsRNA agent of claim 43, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.

46. The dsRNA agent of claim 43-45, wherein the internal positions exclude a cleavage site region of the sense strand.
47. The dsRNA agent of claim 46, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.
48. The dsRNA agent of claim 46, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.
49. The dsRNA agent of claim 43-45, wherein the internal positions exclude a cleavage site region of the antisense strand.
50. The dsRNA agent of claim 49, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.
51. The dsRNA agent of claim 43-45, wherein the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.
52. The dsRNA agent of any one of claims 16-51, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'-end of each strand.
53. The dsRNA agent of claim 52, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.
54. The dsRNA agent of claim 16, wherein the internal positions in the double stranded region exclude a cleavage site region of the sense strand.
55. The dsRNA agent of any one of claims 15-54, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

56. The dsRNA agent of claim 55, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.
57. The dsRNA agent of claim 55, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.
58. The dsRNA agent of claim 55, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.
59. The dsRNA agent of claim 55, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.
60. The dsRNA agent of any one of claims 15-59, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.
61. The dsRNA agent of claim 60, wherein the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl) lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.
62. The dsRNA agent of claim 60, wherein the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.
63. The dsRNA agent of claim 62, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.
64. The dsRNA agent of claim 62, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.
65. The dsRNA agent of claim 64, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

66. The dsRNA agent of any one of claims 15-65, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

67. The dsRNA agent of claim 66, wherein the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

68. The dsRNA agent of any one of claims 15-65, wherein the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

69. The double-stranded iRNA agent of any one of claims 15-68, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

70. The dsRNA agent of any one of claims 15-69, wherein the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

71. The dsRNA agent of any one of claims 15-70, wherein the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

72. The dsRNA agent of any one of claims 15-69, further comprising a targeting ligand that targets a neuronal cell.

73. The dsRNA agent of any one of claims 15-69, further comprising a targeting ligand that targets a liver cell.

74. The dsRNA agent of claim 73, wherein the targeting ligand is a GalNAc conjugate.

75. The dsRNA agent of any one of claims 1-74 further comprising
a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.
76. The dsRNA agent of any one of claims 1-74 further comprising
a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
77. The dsRNA agent of any one of claims 1-74 further comprising
a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
78. The dsRNA agent of any one of claims 1-74 further comprising
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
79. The dsRNA agent of any one of claims 1-74 further comprising

a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,

a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

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

80. The dsRNA agent of any one of claims 1-79, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

81. The dsRNA agent of claim 80, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

82. The dsRNA agent of any one of claims 1-79, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

83. The dsRNA agent of any one of claims 1-79, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

84. A cell containing the dsRNA agent of any one of claims 1-83.

85. A pharmaceutical composition for inhibiting expression of a gene encoding MAPT, comprising the dsRNA agent of any one of claims 1-83.

86. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-83 and a lipid formulation.

87. A pharmaceutical composition for selective inhibition of exon 10-containing MAPT transcripts, comprising the dsRNA agent of any one of claims 1-83.

88. The pharmaceutical composition of any one of claims 85-87, wherein dsRNA agent is in an unbuffered solution.

89. The pharmaceutical composition of claim 88, wherein the unbuffered solution is saline or water.

90. The pharmaceutical composition of any one of claims 85-87, wherein said dsRNA agent is in a buffer solution.

91. The pharmaceutical composition of claim 90, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
92. The pharmaceutical composition of claim 90, wherein the buffer solution is phosphate buffered saline (PBS).
93. A method of inhibiting expression of a MAPT gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92, thereby inhibiting expression of the MAPT gene in the cell.
94. A method of selective inhibition of exon 10-containing MAPT transcripts in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92, thereby selectively degrading exon 10-containing MAPT transcripts in the cell.
95. The method of claim 94, wherein the cell is within a subject.
96. The method of claim 95, wherein the subject is a human.
97. The method of claim 96, wherein the subject has a MAPT-associated disorder.
98. The method of claim 97, wherein the MAPT-associated disorder is a neurodegenerative disorder.
99. The method of claim 98, wherein the neurodegenerative disorder is associated with an abnormality of MAPT gene encoded protein Tau.
100. The method of claim 99, wherein the abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain.
101. The method of claim 99, wherein the neurodegenerative disorder is a familial disorder.
102. The method of claim 99, wherein the neurodegenerative disorder is a sporadic disorder.
103. The method of claim 97 wherein the disorder is selected from the group consisting of tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive

aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

104. The method of any one of claims 93-103, wherein contacting the cell with the dsRNA agent inhibits the expression of MAPT by at least 25%.

105. The method of any one of claims 93-103, wherein inhibiting expression of MAPT decreases Tau protein level in serum of the subject by at least 25%.

106. A method of treating a subject having a disorder that would benefit from reduction in MAPT gene expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92, thereby treating the subject having the disorder that would benefit from reduction in MAPT expression.

107. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in MAPT expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in MAPT expression.

108. The method of claim 106 or 107, wherein the disorder is associated with an abnormality of MAPT gene encoded protein Tau.

109. The method of claim 108, wherein the abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain.

110. The method of claim 108, wherein the disorder is selected from the group consisting of tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal

dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS).

111. The method of any one of claims 107-110, wherein the subject is human.
112. The method of claim 111, wherein the administration of the dsRNA agent, or the pharmaceutical composition, causes a decrease in Tau aggregation in the subject's brain.
113. The method of any one of claims 106-112, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.
114. The method of any one of claims 106-113, wherein the dsRNA agent is administered to the subject intrathecally.
115. The method of any one of claims 106-113, wherein the dsRNA agent is administered to the subject intracisternally.
116. The method of any one of claims 106-115, further comprising determining the level of MAPT in a sample(s) from the subject.
117. The method of claim 116, wherein the level of MAPT in the subject sample(s) is a Tau protein level in a cerebrospinal fluid sample(s).
118. The method of any one of claims 98-117, further comprising administering to the subject an additional therapeutic agent.
119. A kit comprising the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92.
120. A vial comprising the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92.

121. A syringe comprising the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92.

122. An intrathecal pump comprising the dsRNA agent of any one of claims 1-83, or the pharmaceutical composition of any one of claims 85-92.