We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of APOE, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO:1, or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO:2, or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:2, such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

2. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO:1or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO:2, or a nucleotide sequence having at least 90% nucleotide identity to the entire nucleotide sequence of SEQ ID NO:2, such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO:1 or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO:2, or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:2, such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID

NO:1or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of nucleotide sequence of SEQ ID NO:2, or a nucleotide sequence having at least 90% nucleotide sequence identity to the entire nucleotide sequence of SEQ ID NO:2, such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand.

5. The dsRNA agent of any one of claims 1-4, wherein the sense strand and/or the antisense strand is a sense strand and/or an antisense strand selected from the group consisting of any of the sense strands and antisense strands in any one of Tables 2-5 and 7-10.

6. The dsRNA agent of any one of claims 1-5, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of nucleotides 57-79, 62-84, 75-97, 86-108, 207-229, 213-235, 218-240, 898-920, 1128-1150, 637-659 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 1-5, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of nucleotides 57-79, 62-84, 207-229, 1128-1150 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.

8. The dsRNA agent of an one of claims 1-7, 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-1204704, AD-1204705, AD-1204705, AD-1204706 AD-1204707, AD-1204708, AD-1204709, AD-1204710, AD-1204711, AD-1204712, and AD-1204713.

9. The dsRNA agent of an one of claims 1-8, 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-1204704, AD-1204705, AD-1204708, and AD-1204712.

10. The dsRNA agent of any one of claims 1-9, which inhibits the expression of APOE4 but does not substantially inhibit the expression of APOE2 and the expression of APOE3.

11. The dsRNA agent of claim 10, wherein the sense strand and/or the antisense strand is a sense strand and/or an antisense strand selected from the group consisting of any of the sense strands and antisense strands in any one of Tables 7 and 8.

12. The dsRNA agent of any one of claims 1-11, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

13. The dsRNA agent of claim 12, wherein the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent.

14. The dsRNA agent of claim 12 or 13, wherein the lipophilic moiety is conjugated via a linker or a carrier.

15. The dsRNA agent of any one of claims 12-14, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

16. The dsRNA agent of any one of claims 1-15, wherein the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2.

17. The dsRNA agent of claim 16, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

18. The dsRNA agent of any one of claims 1-17, wherein the dsRNA agent comprises at least one modified nucleotide.

19. The dsRNA agent of claim 18, 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

20. The dsRNA agent of claim 18, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

21. The dsRNA agent of any one of claims 18-20, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3’-terminal deoxy-thymidine (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'-hydroxly-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-tetrahydrofurane-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.

22. The dsRNA agent of claim 21, 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 deoxy-thymidine 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.

23. The dsRNA agent of claim 21, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymidine nucleotides (dT).

24. The dsRNA agent of claim 21, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

25. The dsRNA agent of claim 21, further comprising at least one phosphorothioate internucleotide linkage.

26. The dsRNA agent of claim 25, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

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

28. The dsRNA agent of any one of claims 1-27, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

29. The dsRNA agent of any one of claims 1-27, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

30. The dsRNA agent of any one of claims 1-29, wherein the double stranded region is 15-30 nucleotide pairs in length.

31. The dsRNA agent of claim 30, wherein the double stranded region is 17-23 nucleotide pairs in length.

32. The dsRNA agent of claim 30, wherein the double stranded region is 17-25 nucleotide pairs in length.

33. The dsRNA agent of claim 30, wherein the double stranded region is 23-27 nucleotide pairs in length.

34. The dsRNA agent of claim 30, wherein the double stranded region is 19-21 nucleotide pairs in length.

35. The dsRNA agent of claim 30, wherein the double stranded region is 21-23 nucleotide pairs in length.

36. The dsRNA agent of any one of claims 1-35, wherein each strand has 19-30 nucleotides.

37. The dsRNA agent of any one of claims 1-35, wherein each strand has 19-23 nucleotides.

38. The dsRNA agent of any one of claims 1-35, wherein each strand has 21-23 nucleotides.

39. The dsRNA agent of any one of claims 12-38, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

40. The dsRNA agent of claim 39, 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.

41. The dsRNA agent of claim 40, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.

42. The dsRNA agent of claim 40, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.

43. The dsRNA agent of claim 40-42, wherein the internal positions exclude a cleavage site region of the sense strand.

44. The dsRNA agent of claim 43, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

45. The dsRNA agent of claim 43, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

46. The dsRNA agent of claim 40-42, wherein the internal positions exclude a cleavage site region of the antisense strand.

47. The dsRNA agent of claim 46, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

48. The dsRNA agent of claim 40-42, 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.

49. The dsRNA agent of any one of claims 12-48, 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.

50. The dsRNA agent of claim 49, 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.

51. The dsRNA agent of claim 13, wherein the positions in the double stranded region exclude a cleavage site region of the sense strand.

52. The dsRNA agent of any one of claims 12-51, 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.

53. The dsRNA agent of claim 52, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

54. The dsRNA agent of claim 52, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

55. The dsRNA agent of claim 52, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

56. The dsRNA agent of claim 52, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.

57. The dsRNA agent of any one of claims 12-56, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

58. The dsRNA agent of claim 57, 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, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

59. The dsRNA agent of claim 58, 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.

60. The dsRNA agent of claim 59, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

61. The dsRNA agent of claim 59, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

62. The dsRNA agent of claim 61, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

63. The dsRNA agent of any one of claims 12-60, 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.

64. The dsRNA agent of claim 63, 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.

65. The dsRNA agent of any one of claims 12-60, 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.

66. The double-stranded iRNA agent of any one of claims 12-65, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

67. The dsRNA agent of any one of claims 12-66, wherein the lipophilic moeity or targeting ligand is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

68. The dsRNA agent of any one of claims 12-67, 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.

69. The dsRNA agent of any one of claims 12-68, further comprising a targeting ligand that targets a liver tissue.

70. The dsRNA agent of claim 69, wherein the targeting ligand is a GalNAc conjugate.

71. The dsRNA agent of any one of claims 1-70 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.

72. The dsRNA agent of any one of claims 1-70 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.

73. The dsRNA agent of any one of claims 1-70 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.

74. The dsRNA agent of any one of claims 1-70 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.

75. The dsRNA agent of any one of claims 1-70 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.

76. The dsRNA agent of any one of claims 1-75, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

77. The dsRNA agent of claim 76, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

78. The dsRNA agent of any one of claims 1-77, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

79. The dsRNA agent of any one of claims 1-78, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

80. A cell containing the dsRNA agent of any one of claims 1-79.

81. A pharmaceutical composition for inhibiting expression of a gene encoding APOE, comprising the dsRNA agent of any one of claims 1-79.

82. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-79 and a lipid formulation.

83. A method of inhibiting expression of an APOE gene in a cell, the method comprising:
(a) contacting the cell with the dsRNA agent of any one of claims 1-79, or the pharmaceutical composition of claim 81 or 82; and
(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the APOE gene, thereby inhibiting expression of the APOE gene in the cell.

84. The method of claim 83, wherein the cell is within a subject.

85. The method of claim 84, wherein the subject is a human.

86. The method of any one of claims 83-85, wherein the expression of APOE is inhibited by at least 50%.

87. The method of claim 85, wherein the subject meets at least one diagnostic criterion for an APOE-associated neurodegenerative disease.

88. The method of claim 85, wherein the subject has been diagnosed with an APOE-associated neurodegenerative disease.

89. The method of claim 88, wherein the APOE-associated neurodegenerative disease is an amyloid-β-mediated disease.

90. The method of claim 89, wherein the amyloid-β-mediated disease is selected from the group consisting of Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid angiopathy.

91. The method of claim 89, wherein the APOE-associated neurodegenerative disease is a tau-mediated disease.

92. The method of claim 91, wherein the tau-mediated disease is a primary tauopathy or a secondary tauopathy.

93. The method of claim 92, wherein the primary tauopathy is selected from the group consisting of Frontotemporal dementia (FTD), Progressive supranuclear palsy (PSP), Cordicobasal degeneration (CBD), Pick's disease (PiD), Globular glial tauopathies (GGTs), frontotemporal dementia with parkinsonism (FTDP, FTDP-17), Chronic traumatic encelopathy (CTE), Dementia pugilistica, Frontotemporal lobar degeneration (FTLD), Argyrophilic grain disease (AGD), and Primary age-related tauopathy (PART).

94. The method of claim 92, wherein the secondary tauopathy is selected from the group consisting of AD, Creuzfeld Jakob's disease, Down's Syndrome, and Familial British Dementia.

95. A method of treating a subject diagnosed with an APOE-associated neurodegenerative disease, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-79 or the pharmaceutical composition of claim 81 or 82, thereby treating the subject.

96. The method of claim 95, wherein the subject is human.

97. The method of claim 95, wherein treating comprises amelioration of at least on sign or symptom of the disease.

98. The method of claim 96, where treating comprises prevention of progression of the disease.

99. The method of claim 95, wherein the subject has been diagnosed with an APOE-associated neurodegenerative disease.

100. The method of claim 98, wherein the APOE-associated neurodegenerative disease is an amyloid-β-mediated disease.

101. The method of claim 100, wherein the amyloid-β-mediated disease is selected from the group consisting of Alzheimer's's disease, Down's syndrome, and cerebral amyloid angiopathy.

102. The method of claim 98, wherein the APOE-associated neurodegenerative disease is a tau-mediated disease.

103. The method of claim 102, wherein the tau-mediated disease is a primary tauopathy or a secondary tauopathy.

104. The method of claim 103, wherein the primary tauopathy is selected from the group consisting of Frontotemporal dementia (FTD), Progressive supranuclear palsy (PSP), Cordicobasal degeneration (CBD), Pick's disease (PiD), Globular glial tauopathies (GGTs), frontotemporal dementia with parkinsonism (FTDP, FTDP-17), Chronic traumatic encelopathy (CTE), Dementia pugilistica, Frontotemporal lobar degeneration (FTLD), Argyrophilic grain disease (AGD), and Primary age-related tauopathy (PART).

105. The method of claim 103, wherein the secondary tauopathy is selected from the group consisting of AD, Creuzfeld Jakob's disease, Down's Syndrome, and Familial British Dementia.

106. A method of preventing development of an APOE-associated neurodegenerative disease in a subject meeting at least one diagnostic criterion for an APOE-associated neurodegenerative disease, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-79 or the pharmaceutical composition of claim 81 or 82, thereby preventing the development of an APOE-associated neurodegenerative disease in the subject meeting at least one diagnostic criterion for an APOE-associated neurodegenerative disease.

107. The method of claim 106, wherein the subject is human.

108. The method of claim 106, wherein the subject has been diagnosed with an APOE-associated neurodegenerative disease.

109. The method of claim 106, wherein the APOE-associated neurodegenerative disease is an amyloid-β-mediated disease.

110. The method of claim 105, wherein the amyloid-β-mediated disease is selected from the group consisting of Alzheimer's's disease, Down's syndrome, and cerebral amyloid angiopathy.

111. The method of claim 106, wherein the APOE-associated neurodegenerative disease is a tau-mediated disease.

112. The method of claim 111, wherein the tau-mediated disease is a primary tauopathy or a secondary tauopathy.

113. The method of claim 112, wherein the primary tauopathy is selected from the group consisting of Frontotemporal dementia (FTD), Progressive supranuclear palsy (PSP), Cordicobasal degeneration (CBD), Pick's disease (PiD), Globular glial tauopathies (GGTs), frontotemporal dementia with parkinsonism (FTDP, FTDP-17), Chronic traumatic encelopathy (CTE), Dementia pugilistica, Frontotemporal lobar degeneration (FTLD), Argyrophilic grain disease (AGD), and Primary age-related tauopathy (PART).

114. The method of claim 112, wherein the secondary tauopathy is selected from the group consisting of AD, Creuzfeld Jakob's disease, Down's Syndrome, and Familial British Dementia.

115. The method of any one of claims 95-114, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

116. The method of any one of claims 95-115, wherein the dsRNA agent is administered to the subject intrathecally.

117. The method of any one of claims 95-116, further comprising measuring a level of one or more of APOE2, APOE3, and APOE4 protein.

118. The method of any one of claims 95-117, further comprising administering to the subject an additional agent suitable for treatment or prevention of an APOE-associated neurodegenerative disorder.

119. A method of inhibiting expression of an APOE gene in an astrocyte, the method comprising:

(a) contacting the astrocyte with the dsRNA agent of any one of claims 1-79, or the pharmaceutical composition of claim 81 or 82; and

(b) maintaining the astrocyte produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the APOE gene, thereby inhibiting expression of the APOE gene in the astrocyte.

120. The method of claim 119, wherein the astrocyte is within a subject.

121. The method of claim 120, wherein the subject is a human.

122. The method of any one of claims 119-121, wherein the contacting the astrocyte is by inthrathecal administration of the pharmaceutical composition.

123. The method of any one of claims 119-122, wherein the antisense strand of the dsRNA agent 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-1204704, AD-1204705, AD-1204708, and AD-1204712.