APOE GENE THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date of U.S. application No. 62/939999, filed on November 25, 2019, the disclosure of which is incorporated by reference herein.

BACKGROUND

Alzheimer's disease (AD) directly affects 5 million Americans and is rapidly increasing in prevalence and economic impact. Existing drugs have little impact on the underlying disease process and no preventive therapies are currently available. Inheritance of the variant APOE4 conveys a high risk for the development of AD, while inheritance of APOE2 gene is protective, reducing the risk of developing AD by ~50% and delaying the age of onset. APOE4 is associated with increased brain amyloid load and greater memory impairment in AD. Conversely, APOE2 attenuates these effects. Previous studies have shown that adeno-associated virus (AAV) gene delivery of the human APOE2 coding sequence to the CNS of a murine model expressing human APOE4 reduces the amount of amyloid-ß peptide and amyloid burden (Zhao et al. 2016). In humans, the odds ratio of developing AD with E4/E4 homozygous genotype is 14.9 and is reduced to 2.6 in E2/E4 heterozygotes. Recent reports have suggested that APOE4 is associated with abnormal brain function apart from its role in promoting amyloid production.

SUMMARY

The disclosure provides for a gene therapy vector comprising an expression cassette coding for a mammalian apolipoprotein E (APOE) that is protective or includes a substitution, e.g., relative to APOE4, in a region that binds a lipoprotein receptor, e.g., LDLR, or binds heparan sulfate proteoglycan (HSPG), e.g., a region such as that from position 135 to 151. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a residue other than arginine, histidine or lysine at at least one of positions 112, 136, or 158. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a residue other than arginine at positions 112 and 136. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a residue other than arginine at positions 136 and 158. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a residue other than arginine at positions 112, 136 and 158. In one ~~embodiment~~example, the apolipoprotein E is a human apolipoprotein E. In one ~~embodiment~~example, the residue other than arginine is serine, leucine, valine, glycine, isoleucine, alanine, threonine, asparagine, cysteine, or methionine. In one ~~embodiment~~example, the residue other than arginine is serine, threonine, asparagine, cysteine, or glutamine. In one ~~embodiment~~example, position 112 has a cysteine, methionine, valine, threonine, alanine, serine, arginine, glycine or isoleucine. In one ~~embodiment~~example, position 112 has a cysteine. In one ~~embodiment~~example, position 136 has a threonine, cysteine, methionine, arginine or a serine. In one ~~embodiment~~example, position 136 has a serine. In one ~~embodiment~~example, position 158 has a cysteine, methionine, valine, threonine, alanine, serine, arginine, glycine or isoleucine. In one ~~embodiment~~example, position 158 has an arginine or a cysteine. In one ~~embodiment~~example, two of positions 112, 136 or 158 have an arginine. In one ~~embodiment~~example, position 112 does not have an arginine. In one ~~embodiment~~example, position 136 does not have an arginine. In one ~~embodiment~~example, position 158 does not have an arginine. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a Cys at position 112, a Ser at position 136 and a Cys at position 158. In one ~~embodiment~~example, the mammalian APOE in the gene therapy vector has a Cys at position 112, a Ser at

position 136 and a Arg at position 158. In one ~~embodiment~~example, the gene therapy vector is a viral gene therapy vector. In one ~~embodiment~~example, the gene therapy vector is an adenovirus, adeno-associated virus (AAV), retrovirus or lentivirus vector. In one ~~embodiment~~example, the viral gene therapy vector is a rAAV vector. In one ~~embodiment~~example, the AAV vector is pseudotyped, e.g., with AAVrh.10, AAV8, AAV9, AAV5, AAVhu.37, AAVhu.20, AAVhu.43, AAVhu.8, AAVhu.2, or AAV7 capsid. In one ~~embodiment~~example, the AAV vector is pseudotyped with AAVrh.10, AAV8, or AAV5. In one ~~embodiment~~example, the AAV vector is AAV2, AAV5, AAV7, AAV8, AAV9 or AAVrh.10. In one ~~embodiment~~example, the gene therapy vector further comprises a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA. In one ~~embodiment~~example, a second gene therapy vector comprises a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA. In one ~~embodiment~~example, the nucleotide sequence is linked to a second promoter. In one ~~embodiment~~example, the second promoter is a PolIII promoter. In one ~~embodiment~~example, the RNAi comprises miRNA including a plurality of miRNA sequences. In one ~~embodiment~~example, the RNAi comprises siRNA including a plurality of siRNA sequences. In one ~~embodiment~~example, the vector is a plasmid. In one ~~embodiment~~example, the mammalian apolipoprotein gene in the vector has C112, S136 and R158 or a C112, S136 and C158. In one ~~embodiment~~example, a second gene therapy vector comprises a nucleotide sequence having nucleic acid sequences encoding an anti-APOE4 or anti-heparan antibody.

In one aspect, the present disclosure refers to a gene therapy vector comprising an expression cassette coding for a mammalian apolipoprotein E that has a residue other than arginine at at least one of positions 112, 136, or 158, but is not a mammalian apolipoprotein E that has R112, R136 and R158 or a mammalian apolipoprotein E that has C112, R136 and C158, or coding for an antibody that binds to APOE4 or disrupts the binding of APOE to heparan sulfate proteoglycans.

Also provided is a pharmaceutical composition comprising the gene therapy vector. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the gene therapy vectors disclosed herein. In one ~~embodiment~~example, the vector is a viral vector. In one ~~embodiment~~example, the vector is a rAAV vector. In one ~~embodiment~~example, the amount of the vector in the composition is about 1 x 10^{11} to about 1 x 10^{16} genome copies. In one ~~embodiment~~example, the amount of the vector in the composition is about 1 x 10^{12} to about 1 x 10^{15} genome copies. In one ~~embodiment~~example, the amount of the vector in the composition is about 1 x 10^{11} to about 1 x 10^{13} genome copies. In one ~~embodiment~~example, the amount of the vector in the composition is about 1 x 10^{13} to about 1 x 10^{15} genome copies. In one ~~embodiment~~example, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to use of a composition comprising any one of the gene therapy vectors disclosed herein in the manufacture of a medicament for preventing, inhibiting or treating Alzheimer's disease in a mammal. Further provided is a method to prevent, inhibit or treat Alzheimer's disease including preventing or treating one or more symptoms thereof such as dementia, or other tauopathy or cognitive impairment in a mammal. In one ~~embodiment~~example, prior to administration, the mammal has or is at risk of increased amyloid plaque and/or increased tau in the brain, e.g., relative to an age-matched mammal or a mammal with a decreased risk of Alzheimer's disease or other tauopathy or cognitive impairment. In one ~~embodiment~~example, the mammal has cognitive impairment. The use or method includes administering to the mammal an effective amount of a composition comprising the gene therapy vector. In one ~~embodiment~~example, the composition comprises liposomes comprising the vector. In one ~~embodiment~~example, the composition comprises nanoparticles comprising the vector. In one ~~embodiment~~example, the mammal is a E2/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a E3/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E2/E3 heterozygote. In one ~~embodiment~~example, the mammal is a human. In one ~~embodiment~~example, the human is an adult, e.g., over the age of 20 years old, e.g., at least 40, 50 or 60 years old. In one ~~embodiment~~example, the human is a juvenile, e.g., from 10 to 20 years old. In one ~~embodiment~~example, the human is a child, e.g., under the age of 10 years old. In one ~~embodiment~~example, the composition is administered to a human at birth or within 1, 2, 3, 4 or 5 years of birth. In one ~~embodiment~~example, the composition is systemically administered. In one ~~embodiment~~example, the composition is orally administered. In one ~~embodiment~~example, the composition is intravenously administered. In one ~~embodiment~~example, the composition is locally administered. In one ~~embodiment~~example, the composition is injected. In one ~~embodiment~~example, the composition

is administered to the central nervous system. In one ~~embodiment~~example, the composition is administered to the brain. In one ~~embodiment~~example, the composition is a sustained release composition. In one ~~embodiment~~example, administration of the gene therapy vector is effective to prevent or inhibit accumulation of amyloid plaques. In one ~~embodiment~~example, administration of the gene therapy vector is effective to prevent or inhibit tau pathology. In one ~~embodiment~~example, administration of the gene therapy vector is effective to prevent or inhibit accumulation of amyloid plaques and prevent or inhibit tau pathology.

In one aspect, the present disclosure refers to use of a composition comprising any one of the gene therapy vectors disclosed herein in the manufacture of a medicament for preventing, inhibiting or treating a disease associated with APOE4 expression in a mammal. In addition, a method to prevent, inhibit or treat a disease associated with APOE4 expression in a mammal is provided. The use or method includes administering to the mammal an effective amount of a composition comprising the gene therapy vector. In one ~~embodiment~~example, the composition comprises liposomes comprising the vector. In one ~~embodiment~~example, the composition comprises nanoparticles comprising the vector. In one ~~embodiment~~example, the mammal is a E2/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a E3/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a human. In one ~~embodiment~~example, the composition is systemically administered. In one ~~embodiment~~example, the composition is orally administered. In one ~~embodiment~~example, the composition is intravenously administered. In one ~~embodiment~~example, the composition is locally administered. In one ~~embodiment~~example, the composition is injected. In one ~~embodiment~~example, the composition is administered to the central nervous system. In one ~~embodiment~~example, the composition is administered to the brain. In one ~~embodiment~~example, the composition is a sustained release composition.

A method to reduce binding to heparin sulfate proteoglycans in a mammal is provided that includes administering to the mammal an effective amount of a composition comprising the gene therapy vector. In one ~~embodiment~~example, the composition comprises liposomes comprising the vector. In one ~~embodiment~~example, the composition comprises nanoparticles comprising the vector. In one ~~embodiment~~example, the mammal is a E2/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a E3/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a human. In one ~~embodiment~~example, the composition is systemically administered. In one ~~embodiment~~example, the composition is orally administered. In one ~~embodiment~~example, the composition is intravenously administered. In one ~~embodiment~~example, the composition is locally administered. In one ~~embodiment~~example, the composition is injected. In one ~~embodiment~~example, the composition is administered to the central nervous system. In one ~~embodiment~~example, the composition is administered to the brain. In one ~~embodiment~~example, the composition is a sustained release composition.

In one ~~embodiment~~example, the composition is administered via a catheter. In one ~~embodiment~~example, the composition is intraventricularly administered. In one ~~embodiment~~example, the composition is intracranially administered. In one ~~embodiment~~example, the composition is administered to the lumbar region. In one ~~embodiment~~example, the composition is administered to the cisterna magna. In one ~~embodiment~~example, the composition is administered via burr holes to the brain. In one ~~embodiment~~example, the composition is administered below C1-C2.

In one ~~embodiment~~example, the composition is administered so that expression of the encoded gene product, e.g., modified APOE or an antibody that binds heparan, is similar to expression levels of APOE4 in the mammal. In one ~~embodiment~~example, the ratio of secreted vector encoded gene product to secreted APOE4 in the mammal is 1:1. In one ~~embodiment~~example, the ratio of secreted vector encoded gene product to secreted APOE4 in the mammal is 2:1. In one ~~embodiment~~example, the ratio of secreted vector encoded gene product to secreted APOE4 in the mammal is 0.5:1. In one ~~embodiment~~example, the ratio of secreted vector

encoded gene product to secreted APOE4 in the mammal is 0.1:1. In one ~~embodiment~~example, the ratio of secreted vector encoded gene product to secreted APOE4 in the mammal is 3:1. In one ~~embodiment~~example, the levels of expression of the encoded gene product in the mammal prevent or inhibit cognitive decline (deterioration). In one ~~embodiment~~example, the levels of expression of the encoded gene product in the mammal reduce tau tangles and amyloid accumulation. In one aspect, the present disclosure refers to use of a composition comprising any one of the gene therapy vectors disclosed herein in the manufacture of a medicament for preventing or inhibiting cognitive decline in a mammal.

In one aspect, the present disclosure refers to use of a composition comprising any one of the gene therapy vectors disclosed herein in the manufacture of a medicament for preventing, inhibiting or treating a lipid disorder in a mammal. A method to prevent, inhibit or treat a lipid disorder in a mammal is also provided that includes administering to the mammal an effective amount of a composition comprising the gene therapy vector. In one ~~embodiment~~example, the composition comprises liposomes comprising the vector. In one ~~embodiment~~example, the composition comprises nanoparticles comprising the vector. In one ~~embodiment~~example, the mammal is a E2/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a E3/E4 heterozygote. In one ~~embodiment~~example, the mammal is a E4/E4 homozygote. In one ~~embodiment~~example, the mammal is a human. In one ~~embodiment~~example, the composition is systemically administered. In one ~~embodiment~~example, the composition is orally administered. In one ~~embodiment~~example, the composition is intravenously administered. In one ~~embodiment~~example, the composition is locally administered. In one ~~embodiment~~example, the composition is injected. In one ~~embodiment~~example, the composition is administered to the central nervous system. In one ~~embodiment~~example, the composition is administered to the brain. In one ~~embodiment~~example, the composition is a sustained release composition.

In one ~~embodiment~~example, a gene therapy vector comprises an AAV expression vector encoding a human APOE gene modified as described herein and either in *cis* or in *trans* artificial miRNA(s) that target endogenous APOE4. This vector system silences the expression of detrimental endogenous APOE4 in combination with supplementation of the beneficial APOE gene from a gene therapy vector, e.g., an AAV vector. Exemplary microRNA sequences were incorporated in the CAG promoter intron or polyA tail of the vector transgene plasmid coding for the human APOE coding sequence. Alternatively, the microRNA(s) may be inserted between a PolIII promoter, e.g., a U6 promoter, and terminator following the polyA site of the APOE expression cassette. The vector-derived human APOE DNA sequence may include silent nucleotide changes to ensure that it is not suppressed by the microRNAs and can include a tag such as a HA tag for detection, e.g., for pre-clinical detection studies. In one ~~embodiment~~example, the expression construct is packaged into an AAV capsid of a serotype that targets astrocytes and glial cells (for example AAV9 but can be other vectors), the prominent sites of endogenous APOE expression in the CNS.

The vectors described herein may be employed to prevent, inhibit or treat cognitive impairment, dementia, Alzheimer's disease, e.g., autosomal dominant, late onset, or early onset. In one ~~embodiment~~example, the mammal has reduced fibrillar amyloid-beta plaque burden, reduced levels of paired helical filament tau, or decreased neurodegeneration, post-administration of the vector. In one ~~embodiment~~example, the vectors described herein may be employed to prevent, inhibit or treat cognitive impairment, e.g., associated with traumatic brain injury, stroke, transient ischemic attack, dementia, Creutzfeldt-Jakob disease, multiple sclerosis, prion disease, Pick's disease, corticobasal degeneration, Parkinson's disease, Lewy body dementia, Progressive supranuclear palsy; Dementia pugilistica (chronic traumatic encephalopathy); frontotemporal dementia and parkinsonism linked to chromosome 17; Lytico-Bodig disease; Tangle-predominant dementia; Ganglioglioma and gangliocytoma; Meningioangiomatosis; Subacute sclerosing panencephalitis; lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, and lipofuscinosis; Argyrophilic grain disease; or Frontotemporal lobar degeneration.

The vectors described herein may also be employed to prevent, inhibit or treat one or more symptoms associated with hyperlipoproteinemia, e.g., Type I, Type 2, Type 3, Type 4 or Type 5. In one ~~embodiment~~example, the amount of vector administered decreases circulating cholesterol, e.g., decreases VLDL and/or LDL, decreases intermediate density lipoproteins, decreases plasma levels of cholesterol and/or triglycerides, decreases triglycerides containing VLDL, decreases lipid accumulation in the glomerular capillaries, decreases intraglomerular lipoprotein or decreases thrombi.

BRIEF DESCRIPTION OF FIGURES

Figure 1. APOE alleles, prevalence and associated risk of developing Alzheimer's disease.

Figure 2. Exemplary viral gene therapy.

Figure 3. Exemplary route of administration of gene therapy.

Figure 4. Selected amino acid residues for different APOE alleles, prevalence and associated risk of developing Alzheimer's disease.

Figure 5. Nucleotide residues at two positions in different APOE alleles.

Figure 6. APOE3ch mutation.

Figure 7. Impact of APOE3ch mutation.

Figure 8. Affinity of APOE3ch for heparin.

Figure 9. Possible mechanism for APOE or tau binding to HSPGs.

Figure 10. Exemplary gene therapy approaches to prevent, inhibit or treat diseases associated with expression of certain APOE alleles.

Figure 11. Association of APOE alleles with Dominant type III hyperlipoproteinemia and lipoprotein glomerulopathy.

Figure 12. Gene therapy with AAV-mediated delivery of APOE AD decreased risk variants. Based on the knowledge that APOE4 homozygotes have a 15-20-fold increased risk for AD (Reiman et al., 2020; Corder et al., 1993; Hefferman et al., 2016), a therapeutic strategy is employed using an AA V vector to deliver the coding sequence of APOE2 and APOE3 variants with the Christchurch variant to decrease the risk for AD.

Figure 13. APOE variants, the risk for AD, and proposed gene therapy to protect against APOE4. APOE2, 3 and 4 are common variants (Hefferman et al., 2016; ALXFORUM, 2010). APOE3ChC is the variant superimposed on PSEN 1-E290A in the case report of the Christchurch mutation on the APOE3 background protecting from the PSEN 1-E290A dominant variant causing early onset AD19. APOE3ChC and APOE2ChC variants may be therapies to mitigate the high risk of AD in APOE4 homozygotes. The APOE2ChC variant has not been observed in nature, but it may be more effective than APOE3ChC. *Low in the context of PSEN 1-E290A.

Figure 14. Studies supporting the relative effect of APOE3ChC in a female with the PSEN1-E280 mutation. Shown are quantitative data for mean cortical amyloid plaque burden (Pittsburgh Compound 8, PET), inferior temporal cortex PHF tau burden (Floratаucipir PET), hippocampal volume (MRI) and precuneus glucose metabolism (Fludeoxyglucose PET). Black dots- PSEN1 carriers with MCI onset at typical young age; grey dots- PSEN1 carriers that have not yet developed MCI; the subject with PSEN1 carrier + APOE3ChC variant (red dot with arrow). Figure modified from Arboleda-Velasquez et al. (2019).

WHAT IS CLAIMED IS:

1. A gene therapy vector comprising an expression cassette coding for a mammalian apolipoprotein E that has a residue other than arginine at at least one of positions 112, 136, or 158, but is not a mammalian apolipoprotein E that has R112, R136 and R158 or a mammalian apolipoprotein E that has C112, R136 and C158, or coding for an antibody that binds to APOE4 or disrupts the binding of APOE to heparan sulfate proteoglycans.

2. The gene therapy vector of claim 1 wherein the apolipoprotein E is a human apolipoprotein E.

3. The gene therapy vector of claim 1 or 2 wherein the residue other than arginine in the apolipoprotein E is serine, threonine, asparagine, cysteine, or glutamine.

4. The gene therapy vector of any one of claims 1 to 3 wherein position 112 in the apolipoprotein E has a cysteine.

5. The gene therapy vector of any one of claims 1 to 4 wherein position 136 in the apolipoprotein E has an arginine or a serine.

6. The gene therapy vector of any one of claims 1 to 5 wherein position 158 in the apolipoprotein E has an arginine or a cysteine.

7. The gene therapy vector of any one of claims 1 to 3 wherein two of positions 112, 136 or 158 in the apolipoprotein E have an arginine.

8. The gene therapy vector of any one of claims 1 to 3 wherein position 112 in the apolipoprotein E does not have an arginine.

9. The gene therapy vector of any one of claims 1 to 3 wherein position 136 in the apolipoprotein E does not have an arginine.

10. The gene therapy vector of any one of claims 1 to 3 wherein position 158 in the apolipoprotein E does not have an arginine.

11. The gene therapy vector of any one of claims 1 to 10 which is a viral gene therapy vector,

12. The gene therapy vector of claim 11 which is an adenovirus, adeno-associated virus (AAV), retrovirus or lentivirus vector.

13. The gene therapy vector of claim 12 wherein the viral gene therapy vector is a rAAV vector.

14. The gene therapy vector of claim 13 wherein AAV vector is pseudotyped.

15. The gene therapy vector of claim 14 wherein the AAV vector is pseudotyped with AAVrh.10, AAV8, AAV9, AAV5, AAVhu.37, AAVhu.20, AAVhu.43, AAVhu.8, AAVhu.2, or AAV7 capsid.

16. The gene therapy vector of claim 15 wherein the AAV vector is pseudotyped with AAVrh.10, AAV8, or AAV5.

17. The gene therapy vector of any one of claims 13 to 16 wherein the AAV vector is AAV2, AAV5, AAV7, AAV8, AAV9 or AAVrh.10.

18. The gene therapy vector of any one of claims 1 to 17 which further comprises a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA.

19. The gene therapy vector of claim 18 wherein the nucleotide sequence is linked to a second promoter.

20. The gene therapy vector of claim 19 wherein the second promoter is a PolIII promoter.

21. The gene therapy vector of any one of claims 18 to 20 wherein the RNAi comprises miRNA including a plurality of miRNA sequences.

22. The gene therapy vector of any one of claims 18 to 21 wherein the RNAi comprises siRNA including a plurality of siRNA sequences.

23. A pharmaceutical composition comprising the gene therapy vector of any one of claims 1 to 22.

24. The pharmaceutical composition of claim 23 wherein the vector is a viral vector.

25. The pharmaceutical composition of claim 24 wherein the vector is a rAAV vector.

26. The pharmaceutical composition of claim 24 or 25 wherein the amount of the vector is about 1 x 10^{11} to about 1 x 10^{16} genome copies.

27. ~~A method to prevent, inhibit or treat Alzheimer's disease in a mammal, comprising: administering to the mammal an effective amount~~Use of a composition comprising the gene therapy vector of any one of claims 1 to 22 in the manufacture of a medicament for preventing, inhibiting or treating Alzheimer's disease in a mammal.

28. ~~A method to prevent or inhibit cognitive decline in a mammal, comprising: administering to the mammal an effective amount~~Use of a composition comprising the gene therapy vector of any one of

claims 1 to 22 in the manufacture of a medicament for preventing or inhibiting cognitive decline in a mammal.

29. ~~A method to prevent, inhibit or treat a disease associated with APOE4 expression in a mammal, comprising: administering to the mammal an effective amount~~Use of a composition comprising the gene therapy vector of any one of claims 1 to 22 in the manufacture of a medicament for preventing, inhibiting or treating a disease associated with APOE4 expression in a mammal.

30. ~~A method to prevent, inhibit or treat a lipid disorder in a mammal, comprising: administering to the mammal an effective amount~~Use of a composition comprising the gene therapy vector of any one of claims 1 to 22 in the manufacture of a medicament for preventing, inhibiting or treating a lipid disorder in a mammal.

31. The use~~method~~ of claim 27, 28, 29, or 30 wherein the mammal is an E2/E4 heterozygote, an E4/E4 homozygote or a E3/E4 heterozygote.

32. The use~~method~~ of any one of claims 27 to 31 wherein the mammal is a human.

33. The use~~method~~ of any one of claims 27 to 31 wherein the composition is to be systemically administered.

34. The use~~method~~ of any one of claims 27 to 32 wherein the composition is to be injected.

35. The use~~method~~ of any one of claims 27 to 32 or 34 wherein the composition is to be administered to the central nervous system.

36. The use~~method~~ of any one of claims 27 to 32 or 34 wherein the composition is to be administered to the brain.

37. The use~~method~~ of any one of claims 27 to 36 wherein a catheter is to be employed to administer the composition.

38. The use~~method~~ of any one of claims 27 to 37 wherein the composition is a sustained release composition.

39. The use~~method~~ of any one of claims 27 to 38 wherein the vector encodes an apolipoprotein E having C112, S136 and R158 or having C112, S136 and C158.

40. The use~~method~~ of any one of claims 27 to 38 wherein the vector comprises a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA.

41. The use~~method~~ of any one of claims 27 to 38 wherein the mammal is to be further administered a second composition comprising a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA.

42. The use~~method~~ of claim 41 wherein the second composition comprises liposomes.

43. The use~~method~~ of claim 41 wherein the second composition comprises nanoparticles.

44. The use~~method~~ of any one of claims 27 to 38 wherein the mammal is to be further administered a second composition comprising an anti-heparan antibody or an antibody that binds to APOE4 or disrupts the binding of APOE to heparan sulfate proteoglycans, or a nucleotide sequence encoding the antibody.

45. The use~~method~~ of claim 44 wherein a viral vector comprises the nucleotide sequence encoding the antibody.

46. The use~~method~~ of any one of claims 41 to 45 wherein the second composition is to be systemically administered.

47. The use~~method~~ of any one of claims 41 to 45 wherein the second composition is to be locally administered.

48. The use~~method~~ of any one of claims 27 to 47 wherein vector is an AAV vector.