

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 1×10^{11} to about 1×10^{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 of a composition comprising the gene therapy vector of any one of claims 1 to 22.
28. A method to prevent or inhibit cognitive decline in a mammal, comprising: administering to the mammal an effective amount of a composition comprising the gene therapy vector of any one of claims 1 to 22.

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 of a composition comprising the gene therapy vector of any one of claims 1 to 22.
- 5 30. A method to prevent, inhibit or treat a lipid disorder in a mammal, comprising: administering to the mammal an effective amount of a composition comprising the gene therapy vector of any one of claims 1 to 22.
31. The method of claim 27, 28, 29, or 30 wherein the mammal is an E2/E4 heterozygote, an E4/E4
10 homozygote or a E3/E4 heterozygote.
32. The method of any one of claims 27 to 31 wherein the mammal is a human.
33. The method of any one of claims 27 to 31 wherein the composition is systemically administered.
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34. The method of any one of claims 27 to 32 wherein the composition is injected.
35. The method of any one of claims 27 to 32 or 34 wherein the composition
is administered to the central nervous system.
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36. The method of any one of claims 27 to 32 or 34 wherein the composition is administered to the brain.
37. The method of any one of claims 27 to 36 wherein a catheter is employed to administer the
25 composition.
38. The method of any one of claims 27 to 37 wherein the composition is a sustained release composition.
- 30 39. The 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 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.
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41. The method of any one of claims 27 to 38 wherein the mammal is further administered a second composition comprising a nucleotide sequence having RNAi sequences corresponding to APOE4 for inhibition of APOE4 mRNA.
- 40 42. The method of claim 41 wherein the second composition comprises liposomes.
43. The method of claim 41 wherein the second composition comprises nanoparticles.

44. The method of any one of claims 27 to 38 wherein the mammal is 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.

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

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

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

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

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