

WHAT IS CLAIMED IS:

1. A gene therapy vector comprising a first promoter operably linked to a
5 nucleic acid sequence comprising an open reading frame encoding
APOE2 and a 3' untranslated region, and an isolated nucleotide sequence
comprising one or more RNAi nucleic acid sequences for inhibition of
APOE4 mRNA.
- 10 2. The vector of claim 1 wherein the vector comprises the nucleotide
sequence.
3. The vector of claim 2 wherein the nucleotide sequence is inserted 5' or 3'
to the open reading frame.
- 15 4. The vector of claim 2 wherein the nucleotide sequence is inserted 5' and
3' to the open reading frame.
5. The vector of claim 1 wherein the nucleotide sequence is on a different
20 vector.
6. The vector of any one of claims 1 to 5 wherein the isolated nucleotide
sequence comprises a second promoter operably linked to the one or
more RNAi nucleic acid sequences.
- 25 7. The vector of any one of claims 1 to 6 wherein the gene therapy vector is
a viral vector.
8. The vector of claim 5 wherein the different vector is a viral vector.
- 30 9. The vector of claim 7 or 8 wherein the viral vector is an AAV,
adenovirus, lentivirus, herpesvirus or retrovirus vector.
10. The vector of claim 9 wherein the AAV is AAV5, AAV9 or AAVrh10.

11. The vector of any one of claims 1 to 10 wherein the APOE4 is human APOE4.
- 5 12. The vector of any one of claims 1 to 10 wherein the APOE2 is human APOE2.
13. The vector of any one of claims 1 to 13 wherein the first promoter is a PolII promoter.
- 10 14. The vector of claim 6 wherein the second promoter is a PolIII promoter.
- 15 15. The vector of any one of claims 1 to 14 wherein the isolated nucleotide sequence comprises nucleic acid for one or more miRNAs comprising two or more of the RNAi nucleic acid sequences.
16. The vector of any one of claims 1 to 14 wherein the RNAi comprises siRNA including a plurality of siRNA sequences.
- 20 17. The vector of any one of claims 1 to 16 wherein the open reading frame for APOE2 comprises a plurality of silent nucleotide substitutions relative to SEQ ID NO:6.
- 25 18. The vector of claim 17 wherein the plurality of the silent nucleotide substitutions in the APOE2 open reading frame are not in the RNAi nucleic acid sequence in the isolated nucleotide sequence.
- 30 19. The vector of claim 16, 17 or 18 wherein at least 50%, 60%, 70%, 80% or 90% of codons in the open reading frame have a silent nucleotide substitution.
20. The vector of claim 16, 17 or 18 wherein at least 5%, 10%, 20%, 30%, or 40%, of codons in the open reading frame have a silent nucleotide substitution.

21. The vector of any one of claims 1 to 20 wherein the APOE4 that is inhibited has a sequence having at least 80%, 85%, 90%, 95% or more amino acid sequence identity to a polypeptide comprising SEQ ID NO:10.
22. The vector of any one of claims 1 to 21 wherein the APOE2 has a sequence having at least 80%, 85%, 90%, 95% or more amino acid sequence identity to a polypeptide encoded by SEQ ID NO:11.
23. The vector of any one of claims 1 to 22 wherein the one or more RNAi nucleic acid sequences have at least 60%, 70%, 80% 90% or more nucleotide sequence identity to one of SEQ ID Nos. 1-4 or the complement thereof.
24. The vector of claim 1 comprising a first promoter operably linked to a nucleic acid sequence comprising an open reading frame encoding human APOE2 and an isolated nucleotide sequence having one or more RNAi nucleic acid sequences for inhibition of human APOE4 mRNA.
25. The vector of claim 24 wherein the nucleotide sequence is inserted 5' to the open reading frame.
26. The vector of claim 24 wherein the nucleotide sequence is inserted 3' to the open reading frame.
27. The vector of claim 24 wherein the nucleotide sequence is inserted 5' and 3' to the open reading frame.
28. The vector of any one of claims 24 to 27 wherein the isolated nucleotide sequence comprises a second promoter operably linked to the one or more RNAi nucleic acid sequences.
29. A composition comprising the gene therapy vector of any one of claims 1

to 28 and optionally a pharmaceutically acceptable carrier.

30. A method to prevent, inhibit or treat Alzheimer's disease in a mammal,
comprising: administering to the mammal an effective amount of a
5 composition comprising the gene therapy vector of any one of claims 1 to
28 or the composition of claim 29.
31. A method to prevent, inhibit or treat a disease associated with APOE4
expression in a mammal, comprising: administering to the mammal an
10 effective amount of a composition comprising the gene therapy vector of
any one of claims 1 to 28 or the composition of claim 29.
32. The method of claim 30 or 31 wherein the composition comprises
liposomes comprising the gene therapy vector or the different vector, or
15 both.
33. The method of claim 30 or 31 wherein the composition comprises
nanoparticles comprising the gene therapy vector or the different vector,
or both.
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34. The method of claim 30 or 31 wherein the gene therapy vector or the
different vector, or both, comprise a viral vector.
35. The method of any one of claims 30 to 34 wherein the mammal is a
25 E2/E4 heterozygote.
36. The method of any one of claims 30 to 34 wherein the mammal is a
E4/E4 homozygote.
- 30 37. The method of any one of claims 30 to 36 wherein the composition is
systemically administered.
38. The method of any one of claims 30 to 37 wherein the composition is
orally administered.

39. The method of any one of claims 30 to 37 wherein the composition is intravenously administered.
- 5 40. The method of any one of claims 30 to 37 wherein the composition is locally administered.
41. The method of any one of claims 30 to 37 wherein the composition is injected.
- 10 42. The method of any one of claims 30 to 37 wherein the composition is administered to the central nervous system.
43. The method of any one of claims 30 to 37 wherein the composition is administered to the brain.
- 15 44. The method of any one of claims 30 to 43 wherein the composition is a sustained release composition.
- 20 45. The method of any one of claims 30 to 44 wherein the mammal is a human.
46. The method of any one of claims 30 to 45 wherein the RNAi sequences comprise a plurality of miRNA sequences each comprising the one or more RNAi nucleic acid sequences for inhibition of APOE4 mRNA.
- 25 47. The method of claim 46 wherein one of the miRNA sequences in the vector is inserted 5' to the open reading frame and another is inserted 3' to the open reading frame.
- 30 48. The method of any one of claims 30 to 45 wherein the RNAi sequences comprise a miRNA sequence comprising the one or more RNAi nucleic acid sequences for inhibition of APOE4 mRNA.

49. The method of claim 48 wherein the miRNA sequence in the vector is inserted 5' to the open reading frame.
50. The method of claim 48 wherein the miRNA sequence in the vector is inserted 3' to the open reading frame.
51. The method of any one of claims 30 to 45 wherein the vector comprises a PolIII promoter operably linked to the RNAi sequence.
52. The method of any one of claims 30 to 45 wherein a second vector comprises a PolIII promoter operably linked to the RNAi sequence.

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