CLAIMS

We Claim:

1. A recombinant adeno-associated virus (rAAV) vector comprising a nucleic acid sequence encoding an apolipoprotein 2 (APOE2) polypeptide comprising a Christchurch mutation or an apolipoprotein 3 (APOE3) polypeptide comprising a Christchurch mutation, wherein the rAAV vector comprises SEQ ID NO: 8, SEQ ID NO: 21, or SEQ ID NO: 22.

2. The rAAV vector of claim 1, wherein the Christchurch mutation comprises:
an R154S mutation in reference to an unprocessed APOE polypeptide; or
an R136S mutation in reference to mature APOE polypeptide lacking a signal peptide.

3. The rAAV vector of any one of the preceding claims, wherein the rAAV vector is packaged as an rAAV viral vector comprising an AAV capsid protein.

4. The rAAV vector of any one of the preceding claims, wherein the AAV capsid protein is an AAV1 capsid protein, an AAV2 capsid protein, an AAV4 capsid protein, an AAV5 capsid protein, an AAV6 capsid protein, an AAV7 capsid protein, an AAV8 capsid protein, an AAV9 capsid protein, an AAV10 capsid protein, an AAV11 capsid protein, an AAV12 capsid protein, an AAV13 capsid protein, an AAVPHP.B capsid protein, an AAVrh74 capsid protein or an AAVrh10 capsid protein.

5. The rAAV vector of any one of the preceding claims, wherein the AAV capsid protein is an AAVrh10 capsid protein.

6. A pharmaceutical composition comprising the AAV viral vector of claim 3.

7. Use of a pharmaceutical composition according to claim 6 in the manufacture of a medicament for treating Alzheimer's disease in a human subject, wherein the pharmaceutical composition is to be administered in a therapeutically effective amount.

8. The use of claim 7, wherein the therapeutically effective amount of the vector is about 1×10^{10} to about 1×10^{16} genome copies.

9. The use of claim 7, wherein the subject is an APOE2/APOE4 heterozygote, an APOE4/APOE4 homozygote or an APOE3/APOE4 heterozygote.

10. The use of claim 7, wherein the composition is to be administered systemically, intracisternally, via intra cisterna magna, or via CI-C2 administration.

11. The use of claim 7, wherein the pharmaceutical composition is to be administered at a dose of about 5.0×10^9 gc/mL CSF to about 5.0×10^{12} gc/mL CSF.

12. The use of claim 7, wherein the pharmaceutical composition is to be administered at a dose of about:

i) 1.4×10^{10} gc/mL CSF,

ii) 4.4×10^{10} gc/mL CSF, or

iii) 1.4×10^{11} gc/mL CSF.

13. The use of claim 7, wherein the pharmaceutical composition is to be administered at a fixed dose of about 1.4×10^{14} gc.

14. The use of claim 7, wherein the pharmaceutical composition is to be administered in a total volume of about 5 mL, about 10 mL, about 15 mL, or about 20 mL.

15. The use of claim 7, wherein the subject experiences an at least about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100% increase in APOE2 Christchurch or APOE3 Christchurch expression.

16. The use of claim 7, wherein the APOE2 Christchurch or APOE3 Christchurch expression occurs in the central nervous system.

17. The use of claim 7, wherein the APOE2 Christchurch or APOE3 Christchurch expression is measured in the cerebral spinal fluid (CSF).

18. The use of claim 7, wherein following administration of the pharmaceutical composition the expression levels of at least one of T-tau, and P-tau are reduced in the subject relative to a pre-administration baseline.

19. The use of claim 18, wherein the expression levels of T-tau, and/or P-tau are reduced by at least about 5%, at least about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

20. The use of claim 7, wherein following administration of the pharmaceutical composition the amyloid beta 42/amyloid beta 40 ($A\beta_{42/40}$) ratio is increased.

21. The use of claim 20, wherein the $A\beta_{42/40}$ ratio is increased by at least about 5%, at least about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

22. The use of claim 7, wherein prior to treatment with the pharmaceutical composition the subject is to be administered an immunosuppressant.

23. The use of claim 22, wherein the immunosuppressant is prednisone.

24. The use of claim 23, wherein the prednisone is to be administered at a dosage of:
40 mg, once daily 1 week prior to AAV viral vector administration;
40 mg once daily for week 1 through week 2 post-AAV viral vector administration;
30 mg once daily for week 3 post-AAV viral vector administration;
20 mg once daily for week 4 post-AAV viral vector administration;
10 mg once daily for week 5 post-AAV viral vector administration;
5 mg once daily for week 6 post-AAV viral vector administration;
2.5 mg once daily for week 7 post-AAV viral vector administration; and
2.5 mg every other day for week 8 post-AAV viral vector administration.

25. The pharmaceutical composition according to claim 6 for use in therapy.