

CLAIMS

1. A recombinant vector construct comprising a nucleic acid sequence that encodes a functional C1 esterase inhibitor (C1EI) operably linked to a heterologous liver-specific transcription regulatory region, optionally a nucleic acid sequence comprising SEQ ID NO: 1, 10, 11, 12, 13, 59 or 60.
2. The vector construct of claim 1, wherein the mammal is a human and the C1EI is human C1EI.
3. The vector construct of claim 1 or 2 wherein the functional C1EI comprises an amino acid sequence at least 95% identical to amino acids 23-500 of SEQ ID NO: 2.
4. The vector construct of any of the preceding claims, wherein the liver-specific transcription regulatory region comprises a synthetic promoter sequence comprising portions of an hAAT promoter and an HCR enhancer/ApoE enhancer.
5. The vector construct of claim 4, wherein the liver-specific transcription regulatory region comprises (a) a shortened ApoE enhancer sequence at least 90% identical to SEQ ID NO: 16; (b) an alpha anti-trypsin (hAAT) proximal promoter sequence at least 90% identical to SEQ ID NO: 3, and/or (c) one or more enhancers selected from the group consisting of (i) an ApoE/HCR enhancer at least 90% identical to SEQ ID NO: 4.
6. The vector construct of claim 4, wherein the liver-specific transcription regulatory region comprises (a) an α -microglobulin enhancer sequence at least 90% identical to SEQ ID NO: 17, and (b) an alpha anti-trypsin (AAT) proximal promoter at least 90% identical to SEQ ID NO: 3.
7. The vector construct of claim 4, wherein the liver-specific transcription regulatory region comprises a nucleotide sequence at least 80% identical to SEQ ID NO: 5.

8. The vector construct of any of the preceding claims further comprising a polyadenylation signal.
9. The vector construct of claim 8 wherein the polyadenylation signal is a human growth hormone polyadenylation signal or functional fragment thereof.
10. The vector construct of any of the preceding claims further comprising an intron.
11. The vector construct of claim 10 wherein the intron is a composite hAAT/hemoglobin intron sequence.
12. The vector construct of claim 10, wherein the intron comprises a nucleotide sequence at least 80% identical to any of SEQ ID NOs: 6 or 61-69.
13. The vector construct of any of claims 10-12 wherein the nucleic acid sequence that encodes the functional C1 esterase inhibitor (C1EI) comprises the intron.
14. The vector construct of any of the preceding claims further comprising an AAV 5' ITR and/or AAV3' ITR from AAV2.
15. The vector construct of claim 1 that comprises a nucleotide sequence at least 80% identical to any one of SEQ ID NOs: 9, 20-36, 57 or 58.
16. The vector construct of any of the preceding claims that is an rAAV vector construct about 2.7 kb to about 4 kb, or about 4 kb to about 5 kb in size.
17. An rAAV particle comprising the vector construct of any of the preceding claims and an AAV capsid.
18. The rAAV particle of claim 17 that comprises an AAV5 type capsid.

19. The rAAV particle of claim 17 that comprises a simian AAV capsid.
20. The rAAV particle of claim 17 that comprises a baboon-derived AAV capsid.
21. The rAAV of any of claims 17-20 wherein the rAAV particle comprises an AAV capsid with liver tropism.
22. A method of producing an rAAV particle comprising the steps of (a) providing a cell permissive for AAV replication with one or more nucleic acid constructs comprising: (i) a recombinant vector construct comprising (1) at least one AAV ITR, (2) a heterologous liver-specific transcription regulatory region, and (3) a nucleic acid encoding a functional C1EI, (ii) a nucleotide sequence encoding one or more AAV Rep proteins which is operably linked to a promoter that is capable of driving expression of the Rep protein(s) in the cell; and (iii) a nucleotide sequence encoding one or more AAV capsid proteins which is operably linked to a promoter that is capable of driving expression of the capsid protein(s) in the cell; (b) culturing the cell under conditions permitting expression of the Rep and the capsid proteins; and optionally (c) recovering the AAV particle.
23. The method of claim 22, wherein the cell is an insect cell.
24. The method of claim 22, wherein the cell is a mammalian cell.
25. The method of claim 22 wherein the cell is provided with a recombinant vector construct of any of claims 1-16.
26. A population of rAAV particles produced by the method of any one of claims 22-25, optionally enriched for particles comprising full length or nearly full-length vector genomes by steps that reduce the number of empty capsids.

27. A pharmaceutical composition comprising the vector construct of any of claims 1-16 or the rAAV particle of any of claims 17-21 or the population of rAAV particles of claim 26 in an aqueous suspension with a sterile pharmaceutically acceptable excipient.

28. A method of treating hereditary angioedema in a mammal, or treating or preventing any symptom thereof, comprising administering a therapeutically effective amount of the vector construct of any of claims 1-16 or the rAAV particle of any of claims 17-21 or the population of rAAV particles of claim 26 or the pharmaceutical composition of claim 27.

29. A method of treating hereditary angioedema in a mammal, or treating or preventing any symptom thereof, comprising administering a therapeutically effective amount of an rAAV particle comprising a vector construct that comprises a nucleic acid sequence that encodes a functional C1EI, optionally linked to a heterologous transcription regulatory element.

30. The method of claim 29 wherein the C1EI is a functional human C1EI that comprises an amino acid sequence at least 95% identical to amino acids 23-500 of SEQ ID NO: 2.

31. The method of any of claims 28-30, wherein the method reduces the frequency or severity of submucosal or subcutaneous edema in the mammal.

32. A method of expressing C1EI in the liver of a mammal, comprising administering an amount of the vector construct of any of claims 1-16 or the rAAV particle of any of claims 17-21 or the population of rAAV particles of claim 26 or the pharmaceutical composition of claim 27 effective to increase the level of C1EI expression in the liver of the mammal.

33. A method of increasing the level of functional C1EI in the blood of a mammal, comprising administering an amount of the vector construct of any of claims 1-16 or the rAAV particle of any of claims 17-21 or the population of rAAV particles of claim 26 or the pharmaceutical composition of claim 27 effective to increase the level of functional C1EI in the blood of a mammal.

34. A method of treating a deficiency in functional C1EI in a mammal, comprising administering an amount of the vector construct of any of claims 1-16 or the rAAV particle of any of claims 17-21 or the population of rAAV particles of claim 26 or the pharmaceutical composition of claim 27 effective to increase the level of functional C1EI in the blood of a mammal.

35. The method of claim 33 or 34 wherein the amount is effective to increase the level of functional C1EI to at least about 0.4 IU/ml, or 1 IU/ml or higher, or about 16 mg/dL or higher.

36. The method of any of claims 28-35, wherein the rAAV particle or vector construct is administered intravenously.

37. The method of any of claims 28-36, wherein the mammal is concurrently administered corticosteroid therapy with the vector construct or rAAV particle or pharmaceutical composition.

38. The method of any of claims 28-37 wherein the mammal is administered the rAAV particle at a dose ranging from about 1×10^{12} to about 1×10^{15} vg/kg.

39. The vector construct or rAAV particle or pharmaceutical composition of any of the preceding claims for use in treatment of HAE or for use in treating a deficiency in functional C1EI or for use in increasing blood levels of functional C1EI in a mammal.