CLAIMS

1. A polynucleotide comprising a nucleic acid sequence encoding a C1 inhibitor, wherein said polynucleotide comprises a nucleic acid sequence at least 85% identical to SEQ ID NO: 238, 236 or 243 and said C1 inhibitor comprises a sequence at least 93% identical to SEQ ID NO: 181.

2. The polynucleotide of claim 2, wherein said polynucleotide comprises a nucleic acid sequence at least 85% identical to SEQ ID NO: 238 and said C1 inhibitor comprises a sequence at least 95% identical to SEQ ID NO: 181.

3. The polynucleotide of claim 2, wherein said polynucleotide comprises a nucleic acid sequence at least 95% identical to SEQ ID NO: 238 and said C1 inhibitor comprises a sequence at least 95% identical to SEQ ID NO: 181.

4. The polynucleotide of claim 3, wherein said polynucleotide comprises a nucleic acid sequence at least 97% identical to SEQ ID NO: 238 and said C1 inhibitor comprises the sequence of SEQ ID NO: 181.

5. The polynucleotide of claim 4, wherein said polynucleotide comprises a nucleic acid sequence of SEQ ID NO: 238 and said C1 inhibitor comprises the sequence of SEQ ID NO: 181

6. The polynucleotide of any one of claims 2-5, wherein said polynucleotide further comprises a signal peptide sequence at the 5' end of said nucleic acid sequence and said signal peptide sequence is at least 95% identical to the nucleic acid of SEQ ID NO: 264.

7. The polynucleotide of claim 2, wherein the nucleic acid comprises the sequence of any one of SEQ ID NOs: 105-142, 145-147, 156, 171 and 172.

8. A polynucleotide comprising a nucleic acid encoding a variant C1 inhibitor, wherein the nucleic acid is selected from the group consisting of SEQ ID NOs: 143-144, 158, and 165-170.

9. The polynucleotide of claim 2, wherein the nucleic acid comprises a sequence of SEQ ID NO: 119, and wherein the C1 inhibitor comprises the amino acid sequence of SEQ ID NO: 192.

10. The polynucleotide of any one of claims 1-5 and 7-9, comprising a nucleic acid encoding a signal peptide sequence operably linked to the 5' end of the sequence encoding the C1 inhibitor or the variant C1 inhibitor.

11. The polynucleotide acid of claim 10, wherein the signal peptide has the polynucleotide sequence of any one of SEQ ID NOs: 84-103.

12. An expression cassette comprising the polynucleotide of any one of claims 2-11, operably linked to an expression control element, wherein the expression control element is a promoter.

13. The expression cassette of claim 12, further comprising a polyadenylation sequence operably linked to the 3' end of the nucleic acid encoding the C1 inhibitor.

14. The expression cassette of claims 12 or 13, wherein the promoter is a hAAT promoter, the polyadenylation sequence comprises a bovine growth hormone (bGH) polyadenylation sequence and the expression cassette further comprises an ApoE enhancer.

15. The expression cassette of claim 14, wherein the ApoE enhancer comprises the polynucleotide sequence of any one of SEQ ID NOs: 225 and 74-76, the hAAT promoter sequence comprises the polynucleotide sequence of SEQ ID NOs: 79 or 80, and the bGH polyadenylation sequence comprises the polynucleotide sequence of SEQ ID NO: 83.

16. The expression cassette of claim 15, wherein the expression cassette further comprises an intron, wherein the intron comprises a human hemoglobin β (HBB)-derived intron.

17. The expression cassette of claim 16, wherein the human hemoglobin β (HBB)-derived intron sequence comprises the polynucleotide sequence of SEQ ID NOs: 81 or 82.

18. The expression cassette of any one of claims 12-17, further comprising an enhancer selected from the group consisting of ApoE, 2xApoE, 4xApoE, hAAT, WPRE3, and WPRE.

19. The expression cassette of claim 18wherein the enhancer comprises the polynucleotide sequence of any one of SEQ ID NOs: 225, 74-78 and 173-178.

20. The expression cassette of any one of claims 12-18, further comprising one or more response elements selected from the group consisting of an miRNA binding site, a regulated Ire1-dependent decay (RIDD) sequence, an acute phase response element (APRE), a 5' UTR, and a 3' UTR.

21. An adeno-associated virus (AAV) vector comprising the polynucleotide or expression cassette of any one of claims 2-20 .

22. The AAV vector of claim 21, wherein the AAV vector comprises: (a) an AAV capsid, and (b) AAV ITR(s) flanking the 5' and 3' terminus of the expression cassette.

23. The AAV vector of claims 21 or 22, wherein the AAV vector has a capsid serotype comprising a modified or variant AAV VP1, VP2 and/or VP3 capsid having 95% or more sequence identity to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, Rh10, Rh74 (SEQ ID NO: 188), AAV3B, AAV-2i8, SEQ ID NO: 226, SEQ ID NO: 189, SEQ ID NO: 190, and/or SEQ ID NO: 191; wherein the ITRs comprise one or more ITRs of any of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, Rh10, Rh74, or AAV3B.

24. The AAV vector of claim 21 comprising a polynucleotide sequence having at least 99% identity to a sequence selected from the group consisting of SEQ ID NOs: 1-69 and 227-229.

25. The AAV vector of claim 24, wherein said capsid comprises VP1 of SEQ ID NO: 226, VP2 of SEQ ID NO: 189 and VP3 of SEQ ID NO: 190.

26. The AAV vector of claim 25 , wherein said polynucleotide comprises a nucleic acid sequence at least 99% identical to SEQ ID NO: 22, provided that said nucleic acid sequence encodes the sequence of SEQ ID NO: 192.

27. The AAV vector of claims 25 or 26, where said polynucleotide comprises the nucleic acid sequence of SEQ ID NO: 22.

28. The AAV vector of claim 21, comprising the polynucleotide sequence of SEQ ID NO: 22.

29. A pharmaceutical composition comprising the AAV vector of any one of claims 21-28 in a biologically compatible carrier or excipient.

30. The polynucleotide or expression cassette of any one of claims 2-20, or the AAV vector of any one of claims 21-28, or the pharmaceutical composition of claim 29 for use in therapy.

31. Use of a therapeutically effective amount of the polynucleotide or expression cassette of any one of claims 2-20, or the AAV vector of any one of claims 21-28, or the pharmaceutical composition of claim 29 for the manufacture of a medicament for the treatment of hereditary angioedema (HAE).

32. A cell comprising the polynucleotide or expression cassette of any one of claims 1-20.

33. A cell that produces the AAV vector of any one of claims 21-28.

34. A method of producing the AAV vector of any one of claims 21-28, comprising (a) introducing the AAV vector into a packaging helper cell; and (b) culturing the helper cell under conditions to produce the AAV vector.

35. A polypeptide comprising a sequence at least 95%to identical to any of SEQ ID NOs: 215, 216, 217, and 218.

36. The polypeptide of claim 35, wherein the polypeptide comprises the sequence of any of SEQ ID NOs: 215, 216, 217, or 218.

37. A nucleic acid comprising a sequence encoding the polypeptide of claims 35 or 36.