What is Claimed:

1. A nucleic acid sequence encoding human Factor IX (FIX) protein, wherein the coding sequence of said nucleic acid is not naturally occurring, is at least 90% identical to the nucleic acid sequence of SEQ ID NO:10, encodes the same human FIX protein encoded by the nucleic acid sequence of SEQ ID NO:10, has a reduced number of CpG di-nucleotides compared to a wild-type human non-CpG reduced nucleic acid sequence encoding human FIX protein and optionally is interrupted by an intron, or portion thereof.

2. The nucleic acid sequence encoding human FIX protein of claim 1, further comprising an intron, or portion thereof, an expression control element operably linked to said sequence encoding human FIX, one or more adeno-associated virus (AAV) inverted terminal repeats (ITRs) and/or a filler polynucleotide sequence.

3. The nucleic acid sequence encoding human FIX protein of claim 2, wherein the AAV ITR(s) flanks the 5' or 3'end of the sequence encoding human FIX protein, or wherein the filler polynucleotide sequence flanks the 5' or 3'end of the sequence encoding human FIX protein.

4. The nucleic acid sequence encoding human FIX protein of any of claims 1-3, wherein the sequence encoding human FIX protein has 1-5 fewer CpG di-nucleotides than a wild-type human non-CpG reduced nucleic acid sequence encoding human FIX.

5. The nucleic acid sequence encoding human FIX protein of any of claims 1-3, wherein the sequence encoding human FIX protein is devoid of any CpG di-nucleotides.

6. The nucleic acid sequence encoding human FIX protein of any of claims 1-5, wherein the nucleic acid sequence encoding human FIX protein is interrupted by an intron, or portion thereof.

7. The nucleic acid sequence encoding human FIX protein of any of claims 1-6, wherein the nucleic acid sequence encoding human FIX protein comprises a sequence with 95% or more identity to SEQ ID NO:10.

8. A nucleic acid sequence comprising a sequence encoding the same human FIX protein encoded by the nucleic acid sequence of SEQ ID NO:10, wherein the coding sequence of said nucleic acid is not naturally occurring, is at least 90% identical to the nucleic acid sequence of SEQ ID NO:10 and optionally is interrupted by an intron, or portion thereof.

9. The nucleic acid sequence encoding human FIX protein of any of claims 1-4 or 5-8, wherein the intron or portion thereof, if present, comprises the sequence set forth in SEQ ID NO:17.

10. The nucleic acid sequence encoding human FIX protein of any of claims 2-4 or 5-8, wherein the expression control element comprises an enhancer sequence comprising the sequence set forth as SEQ ID NO:14.

11. The nucleic acid sequence encoding human FIX protein of any of claims 2-4 or 5-8, wherein the expression control element comprises a promoter sequence comprising the sequence set forth as SEQ ID NO:15.

12. The nucleic acid sequence encoding human FIX protein of any of claims 2-4 or 5-8, wherein the sequence of the one or more adeno-associated virus (AAV) inverted terminal repeats (ITRs) comprises nucleotides 12-141 from SEQ ID NO:26 and/or nucleotides 3557-3686 from SEQ ID NO:26.

13. The nucleic acid sequence encoding human FIX protein of any of claims 2-4 or 5-8, wherein the filler polynucleotide sequence comprises a sequence set forth as SEQ ID NO:21.

14. The nucleic acid sequence encoding human FIX protein of any of claims 2-4 or 5-8, wherein the expression control element comprises an element that confers expression in liver.

15. The nucleic acid sequence encoding human FIX protein of any of claims 2-4, wherein the expression control element comprises a promoter from human α_1-anti-trypsin (hAAT) gene and/or an enhancer from apolipoprotein E (ApoE) HCR-1 or HCR-2.

16. The nucleic acid sequence encoding human FIX protein of any of claims 1-8, further comprising a poly-adenylation signal sequence located 3’ of the nucleic acid sequence encoding human FIX.

17. The nucleic acid sequence encoding human FIX protein of claim 16, wherein the poly adenylation signal sequence located 3’ of the nucleic acid sequence encoding human FIX comprises a poly-adenylation signal sequence having all CpG di-nucleotides removed therefrom.

18. A plasmid sequence comprising SEQ ID NO:10, 12 or 26.

19. A viral vector comprising the nucleic acid sequence encoding human FIX protein or expression vector comprising the nucleic acid sequence encoding human FIX protein of any of claims 1-8.

20. A viral vector according to claim 19, wherein said viral vector is a lenti- or adeno-viral vector.

21. A viral vector according to claim 19, wherein said viral vector is an adeno-associated viral (AAV) vector.

22. The AAV vector of claim 21, comprising an ITR sequence of any of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 AAV serotypes.

23. The AAV vector of claim 21, wherein the vector comprises a VP1, VP2 and/or VP3 capsid sequence having 90% or more identity to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 VP1, VP2 and/or VP3 sequences.

24. The AAV vector of claim 21, wherein the vector comprises a VP1, VP2 or VP3 capsid sequence selected from any of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 AAV serotypes.

25. The AAV vector of claim 21, wherein the vector comprises a VP1 sequence having 90% or more sequence identity to SEQ ID NO:1; a VP2 sequence having 90% or more sequence identity to SEQ ID NO:2; and/or a VP3 sequence having 90% or more sequence identity to SEQ ID NO:3.

26. The AAV vector of claim 21, wherein the vector comprises a VP1 capsid comprising an amino acid substitution at any one of amino acid positions 195, 199, 201 or 202, of the sequence set forth as SEQ ID NO:1, or an amino acid substitution of an arginine for a lysine in the sequence set forth as SEQ ID NO:1.

27. The AAV vector of claim 21, wherein the vector comprises a VP1 capsid comprising residues A, V, P or N amino acids at any one of amino acid positions 195, 199, 201 or 202 of the sequence set forth as SEQ ID NO:1.

28. The AAV vector of claim 21, wherein the vector comprises a VP1 capsid comprising an A residue at amino acid position 195; a V residue at amino acid positions 199, a P residue at

amino acid position 201, or an N residue at amino acid position 202 of the sequence set forth as SEQ ID NO:1.

29. The AAV vector of claim 21, wherein the vector comprises a VP1 capsid comprising any two, three or four of an A residue at amino acid position 195; a V residue at amino acid positions 199, a P residue at amino acid position 201, or an N residue at amino acid position 202 of the sequence set forth as SEQ ID NO:4.

30. The AAV vector of claim 21, wherein the vector comprises a sequence comprising any of SEQ ID NOs:4-9.

31. A pharmaceutical composition comprising a viral vector of any of claims 19-30.

32. A pharmaceutical composition according to claim 31, further comprising empty capsid AAV.

33. A pharmaceutical composition according to claim 32 wherein said empty capsid is selected from serotype AAV AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 and AAV11.

34. The nucleic acid sequence, or virus vector of any of claims 1-33 for use in the treatment of hemophilia B in a subject.

35. Use of the nucleic acid sequence, or virus vector of any of claims 1-33 in the manufacture of a medicament for the treatment of hemophilia B in a subject.

36. The nucleic acid sequence, or virus vector for use according to claim 34, or the use according to claim 35, wherein said FIX protein is expressed in a cell, tissue or organ of said subject.

37. A recombinant AAV (rAAV) vector for treating hemophilia B, comprising a capsid and a genome, wherein said capsid comprises a VP1 protein having the amino acid sequence of SEQ ID NO:4; and wherein said genome is single-stranded and comprises the following elements in 5’ to 3’ order:

(a) a first AAV ITR,

(b) an enhancer from ApoE HCR-1,

(c) a promoter from AAT,

(d) the nucleic acid sequence of claim 8 encoding human Factor IX Padua,

(e) a polyadenylation signal sequence; and

(f) a second AAV ITR.

38. The rAAV of claim 37, wherein said first and/or second AAV ITR is from AAV2, and wherein nucleic acid sequence encoding human Factor IX Padua is interupted by an intron, or portion thereof.

39. The rAAV of claim 38, wherein said intron is Intron A from the human FIX gene, and wherein said polyadenylation signal sequence is from the bovine growth hormone gene.

40. The rAAV vector of claim 39, wherein

(a) the nucleic acid sequence of the first AAV2 ITR consists of nucleotides 12-141 of SEQ ID NO:26,

(b) the nucleic acid sequence of said ApoE HCR-1 enhancer consists of nucleotides 152-472 of SEQ ID NO:12,

(c) the nucleic acid sequence of said ATT promoter consists of nucleotides 482-878 of SEQ ID NO:12,

(d) the nucleic acid sequence of said nucleic acid encoding human Factor IX Padua variant consists of nucleotides 908-3731 of SEQ ID NO:12,

(e) the nucleic acid sequence of said polyadenylation signal sequence consists of nucleotides 3820-4047 of SEQ ID NO:12; and

(f) the nucleic acid sequence of said second AAV2 ITR consists of nucleotides 3557-3686 of SEQ ID NO:26.

41. The rAAV vector of claim 39, wherein the genome comprises a nucleic acid sequence corresponding to nucleotides 142-4096 of SEQ ID NO:12.

42. The rAAV vector of any one of claims 37-41 for use in the treatment of hemophilia B.

43. Use of the rAAV vector of any one of claims 37-41 in the manufacture of a medicament for the treatment of hemophilia B.

44. The rAAV vector for use according to claim 42, or the use according to claim 43, wherein the hemophilia B is severe hemophilia B, and wherein said treatment is effective to reduce the hemophilia symptoms from severe to those of moderate or mild hemophilia B.

45. A packaging cell comprising the nucleic acid sequence encoding human FIX protein of claim 1 or 8.

46. The packaging cell of claim 45, further comprising AAV rep protein, AAV capsid protein and adenovirus helper protein(s).

47. A method of producing an AAV vector comprising the nucleic acid sequence from 142-4096 of SEQ ID NO:12, comprising culturing the packaging cell of claim 46 under conditions allowing packaging of the nucleic acid sequence from 142-4096 of SEQ ID NO:12 into AAV particles thereby producing AAV vector.

48. The method of claim 47, further comprising purifying or isolating the AAV vector so produced.

49. An AAV vector produced by the method of claim 47.

50. An isolated or purified AAV vector produced by the method of claim 48.

51. The nucleic acid of claim 1 or 8, wherein the sequence of said nucleic acid is any one of the following: at least 95% identical to SEQ ID NO:10, at least 96% identical to SEQ ID NO:10, at least 97% identical to SEQ ID NO:10, at least 98% identical to SEQ ID NO:10 and at least 99% identical to SEQ ID NO:10.