CLAIMS

1. A recombinant adeno-associated virus (rAAV) vector genome comprising:

(a) a promoter; and

(b) a codon optimized sequence encoding a hPAH wherein the codon optimized PAH sequence comprises SEQ ID NO: 7 or a sequence having at least 95% sequence identity to SEQ ID NO: 7; and

(c) an AAV 5' ITR sequence and an AAV 3' ITR sequence.

2. The rAAV vector genome of claim 1, wherein the codon optimized hPAH sequence comprises a sequence having at least 98% sequence identity to SEQ ID NO: 7.

3. The rAAV vector genome of claim 1, wherein the codon optimized hPAH sequence comprises SEQ ID NO: 8.

4. The rAAV vector genome of claim 1, wherein the codon optimized hPAH sequence comprises SEQ ID NO: 13.

5. The rAAV vector genome according to claim 1, wherein the codon optimized hPAH sequence comprises SEQ ID NO: 7.

6. The rAAV vector genome according to claim 1, wherein the codon optimized hPAH sequence consists of SEQ ID NO: 7.

7. The rAAV vector genome according to claim 1, wherein the AAV 5' ITR and/or AAV3' ITR is from AAV2.

8. The rAAV vector genome according to any one of claims 1-7, wherein the promoter is a liver-specific promoter.

9. The rAAV vector genome according to any one of claims 1-8, wherein the promoter comprises a synthetic promoter, a constitutive promoter, a regulatable promoter, or a promoter responsive to physiologic cues.

10. The rAAV vector genome according to claim 8, wherein the promoter is a thyroxine binding globulin (TBG) promoter, a transthyretin (TTR) promoter, a human albumin (humAlb) promoter; a Liver Specific promoter (LSP), or a hepatitis B virus core promoter.

11. The rAAV vector genome according to any one of claims 1-8, wherein the promoter is synthetic promoter comprising portions of an hAAT promoter, a hepatic control region (HCR) enhancer, and an ApoE enhancer.

12. The rAAV vector genome according to any one of claims 1-8, wherein the promoter comprises SEQ ID NO: 6 or a sequence having at least 80% sequence identity to SEQ ID NO: 6.

13. The rAAV vector genome according to claim 12, wherein the promoter comprises a sequence having at least 85% sequence identity to SEQ ID NO: 6.

14. The rAAV vector genome according to claim 12, wherein the promoter comprises of a sequence having at least 90% sequence identity to SEQ ID NO: 6.

15. The rAAV vector genome according to claim 12, wherein the promoter comprises of a sequence having at least 95% sequence identity to SEQ ID NO: 6.

16. The rAAV vector genome according to claim 12, wherein the promoter comprises SEQ ID NO: 6.

17. The rAAV vector genome according to any one of claims 1-16, wherein the vector genome further comprises an intron.

18. The rAAV vector genome according to claim 17, wherein the intron is a composite globin/A1AT intron sequence.

19. The rAAV vector genome according to claim 17, wherein the intron sequence comprises SEQ ID NO: 14 or a sequence having at least 80% sequence identity to SEQ ID NO: 14.

20. The rAAV vector genome according to claim 19, wherein the intron sequence comprises a sequence having at least 85% sequence identity to SEQ ID NO: 14.

21. The rAAV vector genome according to claim 19, wherein the intron sequence comprises a sequence having at least 90% sequence identity to SEQ ID NO: 14.

22. The rAAV vector genome according to claim 19, wherein the intron sequence comprises a sequence having at least 95% sequence identity to SEQ ID NO: 14.

23. The rAAV vector genome according to claim 19, wherein the intron sequence comprises SEQ ID NO: 14.

24. The rAAV vector genome according to any one of claims 1-23, wherein the vector genome further comprises a polyadenylation signal sequence.

25. The rAAV vector genome according to claim 24, wherein the polyadenylation signal sequence is a bovine growth hormone (bGH) poly(A), SV40 late poly(A), rabbit beta-globin (rBG) poly(A), or thymidine kinase (TK) poly(A) sequence.

26. The rAAV vector genome according to claim 24, wherein the polyadenylation signal is a bovine growth hormone polyadenylation signal (bGH).

27. The rAAV vector genome according to any one of claims 1-26, wherein the vector genome is 2 kb to 3 kb, 3 kb to 4 kb, or 4 kb to 5 kb in size.

28. The rAAV vector genome according to claim 1, wherein the vector genome sequence comprises (a) SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21; or (b) a sequence having at least 80% sequence identity to SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

29. The rAAV vector genome according to claim 1, wherein the vector genome sequence comprises SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

30. The rAAV vector genome according to claim 1, wherein the vector genome sequence comprises a sequence having at least 80% sequence identity to SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

31. The rAAV vector genome according to claim 1, wherein the vector genome comprises a sequence having at least 85% sequence identity to SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

32. The rAAV vector genome according to claim 1, wherein the vector genome comprises a sequence having at least 90% sequence identity to SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

33. The rAAV vector genome according to claim 1, wherein the vector genome comprises a sequence having at least 95% sequence identity to SEQ ID NO: 16; SEQ ID NO: 18; SEQ ID NO: 20; or SEQ ID NO: 21.

34. The rAAV vector genome according to claim 1, wherein the vector genome comprises SEQ ID NO: 16.

35. The rAAV vector genome according to claim 1, wherein the vector genome sequence comprises SEQ ID NO: 18.

36. A recombinant adeno-associated virus (rAAV) particle comprising an AAV capsid and the vector genome of any one of claims 1-35.

37. The rAAV particle according to claim 36, wherein the AAV capsid is an AAV5 capsid.

38. An isolated nucleic acid molecule comprising a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO: 7 and which encodes functional PAH.

39. An isolated nucleic acid molecule comprising a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO: 7 and which encodes functional hPAH.

40. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 7 and which encodes functional hPAH.

41. A method of producing an rAAV particle of claim 36 or 37, comprising the steps of (a) culturing in cell culture a cell transfected or transduced with a rAAV vector genome of any one of claims 1-35, wherein the cell expresses AAV capsid and rep proteins; and (b) recovering rAAV particles from the supernatant of the cell.

42. The method of claim 41, wherein said cell is an insect cell.

43. The method of claim 42, wherein said insect cell is an SF9 cell or subclone thereof.

44. The method of any one of claims 41-43, wherein the transfection or transduction of said cell with the rAAV vector genome was accomplished by infection of said cell by a baculovirus comprising said rAAV vector genome.

45. The method of any one of claims 41-44, wherein the cell has been co-transfected or co-transduced with a second vector comprising AAV rep and cap genes.

46. A pharmaceutical composition comprising the rAAV vector genome of any one of claims 1-35, or the rAAV particle of claim 36 or 37, and a pharmaceutically acceptable carrier.

47. Use of the rAAV particle of claim 36 or 37 in the manufacture of a medicament for the expression of PAH protein in a subject suffering from phenylketonuria (PKU).

48. Use of the rAAV vector genome of any one of claims 1-35, the rAAV particle of claim 36 or 37, or the pharmaceutical composition of claim 46, for the manufacture of a medicament for the treatment of PKU in a subject.

49. The use of claim 47 or 48, wherein the rAAV particle is in an aqueous suspension at a concentration of 1 x 10^{12} to 1 x 10^{15} vg/kg.

50. The use of any one of claims 47-49, wherein the subject is a human.