

We claim:

1. A method for correcting a mutation in a beta globin (HBB) gene in a cell, the method comprising transducing the cell with a replication-defective adeno-associated virus (AAV) comprising:
 - a) an AAV capsid comprising an AAV Clade F capsid protein; and
 - b) a correction genome comprising: (i) an editing element for editing a target locus in a target gene; (ii) a 5' homology arm nucleotide sequence 5' of the editing element having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence 3' of the editing element having homology to a second genomic region 3' to the target locus,wherein the cell is transduced without co-transducing or co-administering an exogenous nuclease or a nucleotide sequence that encodes an exogenous nuclease.
2. The method of claim 1, wherein the cell is a pluripotent stem cell.
3. The method of claim 1, wherein the cell is a hematopoietic stem cell.
4. The method of claim 1, wherein the cell is a CD34⁺ hematopoietic stem cell.
5. The method of any one of claims 1-4, wherein the cell is in a mammalian subject and the AAV is administered to the subject in an amount effective to transduce the cell in the subject.
6. A method for treating a subject having a disease or disorder associated with an HBB gene mutation, the method comprising:
 - a) transducing an erythrocyte progenitor cell from the subject *ex vivo* with a replication-defective AAV comprising:
 - (i) an AAV capsid comprising an AAV Clade F capsid protein; and
 - (ii) a correction genome comprising: (A) an editing element for editing a target locus in a target gene; (B) a 5' homology arm nucleotide sequence 5' of the editing element having homology to a first genomic region 5' to the target locus; and (C) a 3' homology arm nucleotide sequence 3' of the editing element having homology to a second genomic

- region 3' to the target locus, thereby obtaining a transduced cell having a corrected HBB gene, and;
- b) administering the transduced cell to the subject,
wherein the cell is transduced without co-transducing an exogenous nuclease or a nucleotide
5 sequence that encodes an exogenous nuclease.
7. The method of claim 6, wherein the erythrocyte progenitor cell is a pluripotent stem cell.
- 10 8. The method of claim 6, wherein the erythrocyte progenitor cell is a hematopoietic stem cell.
9. The method of claim 6, wherein the erythrocyte progenitor cell is CD34⁺ hematopoietic stem cell.
- 15 10. A method for treating a subject having a disease or disorder associated with an HBB gene mutation, the method comprising administering to the subject an effective amount of a replication-defective AAV comprising:
- a) an AAV capsid comprising an AAV Clade F capsid protein; and
- 20 b) a correction genome comprising: (i) an editing element for editing a target locus in a target gene; (ii) a 5' homology arm nucleotide sequence 5' of the editing element having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence 3' of the editing element having homology to a second genomic region 3' to the target locus,
- 25 without co-administering an exogenous nuclease or a nucleotide sequence that encodes an exogenous nuclease.
11. The method of any one of claims 6-10, wherein the disease or disorder is thalassemia or sickle cell disease.
- 30 12. The method of any one of claims 6-10, wherein the subject is a human subject.
13. The method of any one of the preceding claims, wherein the target gene is the HBB gene.

14. The method of any one of the preceding claims, wherein the target locus is at a nucleotide point mutation, insertion or deletion in the HBB gene.
- 5 15. The method of claim 14, wherein the nucleotide point mutation or deletion in the HBB gene is selected from the group consisting of G at position -87, G at position -31, A at position -30, G at position -29, G at position -28, T at position -10, C at position 1, A at position 1, G at position 2, deletion of C and T at positions 17 and 18, A at position 19, deletion of A at position 20, T at position 20, deletion of A and A at positions 25 and 26, addition of G after position 26, A at position 47, A at position 48, deletion of C at position 10 51, A at position 52, G at position 58, G at position 59, A at position 79, T at position 82, addition of C after position 84, T at position 93, A at position 93, C at position 97, C at position 98, G at position 202, G at position 208, C at position 222, deletion of T at position 241 or 242, deletion of T and T and C and T at positions 254 to 257, T at position 260, deletion of C at position 264 or 265, addition of A after position 343, deletion of G and T at 15 positions 399 and 400, T at position 401, addition of A after position 417, A at position 446, T at position 1099, A at position 1293, T at position 1344.
16. The method of claim 14 or 15, wherein the editing element comprises a portion of the 20 wild-type HBB gene that corresponds to the mutation.
17. The method of any one of claims 1-16, wherein the editing element comprises the coding regions of one or more exons of an HBB gene.
- 25 18. The method of any one of claims 1-16, wherein the editing element comprises a portion of an HBB gene comprising the coding region of exon 1, the entire intron 1, the entire exon 2, the entire intron 2, and the coding region of exon 3.
19. The method of claim 17 or 18, wherein the coding regions have been silently altered 30 to be less than 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% identical to the corresponding exons of the wild-type HBB gene.
20. The method of claim 19, wherein the editing element comprises at least one of the nucleotide sequences selected from the group consisting of SEQ ID NOs: 43-46 and 105-107.

21. The method of any one of claims 1-12, wherein the target locus is AAVS1.
22. The method of any one of claims 1-16 and 21, wherein the editing element comprises
5 a nucleotide sequence encoding SEQ ID NO: 48 or a portion thereof.
23. The method of claim 22, wherein the nucleotide sequence encoding SEQ ID NO: 48 consists of nucleotides 4 to 444 of SEQ ID NO: 27.
- 10 24. The method of claim 22, wherein the nucleotide sequence encoding SEQ ID NO: 48 is silently altered to be less than 70%, 75%, 80%, 85%, or 90% identical to nucleotides 4 to 444 of SEQ ID NO: 27.
25. The method of claim 24, wherein the nucleotide sequence encoding SEQ ID NO: 48
15 consists of the sequence of SEQ ID NO: 47 or 100.
26. The method of claim 22, wherein the nucleotide sequence encoding SEQ ID NO: 48 consists of a stuffer-inserted coding sequence of the HBB gene.
- 20 27. The method of any one of claims 22-26, wherein the target locus is the internucleotide bond between nucleotide 3 and nucleotide 4 of the target gene, whereby integration of the editing element at the target locus results in the target locus comprising an HBB coding sequence or stuffer-inserted coding sequence starting with the start codon of the target gene.
- 25 28. The method of any one of claims 22-26, wherein the editing element comprises an HBB coding sequence or stuffer-inserted coding sequence consisting of 5' to 3' a start codon and the nucleotide sequence encoding SEQ ID NO: 48, or a portion of the HBB coding sequence or stuffer-inserted coding sequence.
- 30 29. The method of claim 28, wherein the target locus is in an intron of the target gene, and wherein the editing element comprises 5' to 3' a splice acceptor site, a ribosomal skipping element, and an HBB coding sequence or stuffer-inserted coding sequence.
30. The method of claim 29, wherein the target locus is in intron 1 of the HBB gene.

31. The method of claim 28, wherein the target locus is adjacently 3' to a coding nucleotide of the target gene, and wherein the editing element comprises 5' to 3' a ribosomal skipping element and an HBB coding sequence or stuffer-inserted coding sequence.
- 5 32. The method of claim 31, wherein the target locus is the stop codon of a wild-type target gene or the corresponding nucleotides of a mutant target gene.
33. The method of any one of claims 22-32, wherein the editing element further
10 comprises an exogenous polyadenylation sequence 3' to the nucleotide sequence encoding SEQ ID NO: 48.
34. The method of any one of the preceding claims, wherein the editing element further comprises a restriction endonuclease site not present in the target gene.
- 15 35. The method of any one of the preceding claims, wherein the editing element comprises the nucleotide sequence set forth in any one of SEQ ID NOs: 23-28.
36. The method of any one of the preceding claims, wherein the 5' homology arm
20 nucleotide sequence is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the first genomic region.
37. The method of any one of the preceding claims, wherein the 3' homology arm
25 nucleotide sequence is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the second genomic region.
38. The method of any one of the preceding claims, wherein the first genomic region is located in a first editing window, and the second genomic region is located in a second editing window.
- 30 39. The method of claim 38, wherein the first and second editing windows are different.
40. The method of claim 38, wherein the first and second editing windows are the same.

41. The method of any one of claims 38-40, wherein the first editing window consists of the nucleotide sequence set forth in SEQ ID NO: 101, 102, or 103.
42. The method of any one of claims 38-41, wherein the second editing window consists
5 of the nucleotide sequence set forth in SEQ ID NO: 101, 102, or 103.
43. The method of any one of claims 38-42, wherein the first genomic region consists of the nucleotide sequence set forth in SEQ ID NO: 101.
- 10 44. The method of any one of claims 38-43, wherein the second genomic region consists of the nucleotide sequence set forth in SEQ ID NO: 102.
45. The method of any one of the preceding claims, wherein the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 101.
- 15 46. The method of any one of the preceding claims, wherein the 3' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 102.
47. The method of any one of the preceding claims, wherein each of the 5' and 3'
20 homology arm nucleotide sequences independently has a length of about 100 to about 2000 nucleotides.
48. The method of any one of the preceding claims, wherein the correction genome further comprises a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the 5'
25 homology arm nucleotide sequence, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the 3' homology arm nucleotide sequence.
49. The method of claim 48, wherein the 5' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:18, and the 3' ITR nucleotide sequence has at least 95%
30 sequence identity to SEQ ID NO:19.
50. The method of claim 48, wherein the 5' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:20, and the 3' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:21.

51. The method of any one of the preceding claims, wherein the correction genome comprises the nucleotide sequence set forth in any one of SEQ ID NOs: 29-42 and 104.

52. The method of any one of the preceding claims, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of amino acids 203-736 of SEQ ID NO:2, wherein: the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.

53. The method of claim 52, wherein:

- (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G;
- (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;
- (c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R;

- (d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or
- (e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.

54. The method of claim 52, wherein the capsid protein comprises the amino acid sequence of amino acids 203-736 of SEQ ID NO: 2, 3, 4, 6, 7, 10, 11, 12, 13, 15, 16, or 17.

55. The method of any one of the preceding claims, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of amino acids 138-736 of SEQ ID NO: 2, wherein: the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 2 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.

56. The method of claim 55, wherein:
- (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G;
- 5 (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;
- 10 (c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R;
- (d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or
- 15 (e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.
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57. The method of claim 55, wherein the capsid protein comprises the amino acid sequence of amino acids 138-736 of SEQ ID NO: 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17.
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58. The method of any one of the preceding claims, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of amino acids 1-736 of SEQ ID NO:2, wherein: the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 2 is T; the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 68 of SEQ ID NO: 2 is V; the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 2 is L; the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 2 is D; the amino acid in the
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capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.

59. The method of claim 58, wherein:

(a) the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 2 is T, and the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q;

(b) the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 2 is I, and the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is Y;

(c) the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K;

(d) the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 2 is L, and the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S;

(e) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G;

(f) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is

- N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;
- (g) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R;
- (h) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or
- (i) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.
60. The method of claim 58, wherein the capsid protein comprises the amino acid sequence of amino acids 1-736 of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.
61. The method of any one of the preceding claims, wherein the integration efficiency of the editing element into the target locus is at least 1% when the AAV is contacted *in vitro* in the absence of an exogenous nuclease with a population of CD34⁺ human stem cells under standard AAV transduction conditions.
62. The method of any one of the preceding claims, wherein the allelic frequency of integration of the editing element into the target locus is at least 0.5% when the AAV is contacted *in vitro* in the absence of an exogenous nuclease with a population of CD34⁺ human stem cells under standard AAV transduction conditions.
63. A replication-defective adeno-associated virus (AAV) comprising:
- a) an AAV capsid comprising an AAV Clade F capsid protein; and
 - b) a correction genome comprising (i) an editing element for editing a target locus in a target gene, (ii) a 5' homology arm nucleotide sequence 5' of the editing element having homology to a first genomic region 5' to the target locus, and (iii) a 3' homology arm

nucleotide sequence 3' of the editing element having homology to a second genomic region 3' to the target locus.

64. The AAV of claim 63, wherein the target gene is the HBB gene.

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65. The AAV of claim 63 or 64, wherein the target locus is at a nucleotide point mutation or deletion in the HBB gene.

66. The AAV of claim 65, wherein the nucleotide point mutation or deletion in the HBB
10 gene is selected from the group consisting of G at position -87, G at position -31, A at
position -30, G at position -29, G at position -28, T at position -10, C at position 1, A at
position 1, G at position 2, deletion of C and T at positions 17 and 18, A at position 19,
deletion of A at position 20, T at position 20, deletion of A and A at positions 25 and 26,
addition of G after position 26, A at position 47, A at position 48, deletion of C at position
15 51, A at position 52, G at position 58, G at position 59, A at position 79, T at position 82,
addition of C after position 84, T at position 93, A at position 93, C at position 97, C at
position 98, G at position 202, G at position 208, C at position 222, deletion of T at position
241 or 242, deletion of T and T and C and T at positions 254 to 257, T at position 260,
deletion of C at position 264 or 265, addition of A after position 343, deletion of G and T at
20 positions 399 and 400, T at position 401, addition of A after position 417, A at position 446,
T at position 1099, A at position 1293, T at position 1344.

67. The AAV of claim 65 or 66, wherein the editing element comprises a portion of the
wild-type HBB gene that corresponds to the mutation.

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68. The AAV of any one of claims 63-67, wherein the editing element comprises the
coding regions of one or more exons of an HBB gene.

69. The AAV of any one of claims 63-68, wherein the editing element comprises a
30 portion of an HBB gene comprising the coding region of exon 1, the entire intron 1, the entire
exon 2, the entire intron 2, and the coding region of exon 3.

70. The AAV of claim 68 or 69, wherein the coding regions have been silently altered to be less than 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% identical to the corresponding exons of the wild-type HBB gene.
- 5 71. The AAV of claim 70, wherein the editing element comprises at least one of the nucleotide sequences selected from the group consisting of SEQ ID NOs: 43-46 and 105-107.
72. The AAV of claim 63, wherein the target locus is AAVS1.
- 10 73. The AAV of any one of claims 63-66 and 72, wherein the editing element comprises a nucleotide sequence encoding SEQ ID NO: 48 or a portion thereof.
74. The AAV of claim 73, wherein the nucleotide sequence encoding SEQ ID NO: 48 consists of nucleotides 4 to 444 of SEQ ID NO: 27.
- 15 75. The AAV of claim 73, wherein the nucleotide sequence encoding SEQ ID NO: 48 is silently altered to be less than 70%, 75%, 80%, 85%, or 90% identical to nucleotides 4 to 444 of SEQ ID NO: 27.
- 20 76. The AAV of claim 75, wherein the nucleotide sequence encoding SEQ ID NO: 48 consists of the sequence of SEQ ID NO: 47 or 100.
77. The AAV of claim 73, wherein the nucleotide sequence encoding SEQ ID NO: 48 consists of a stuffer-inserted coding sequence of the HBB gene.
- 25 78. The AAV of any one of claims 73-77, wherein the target locus is the internucleotide bond between nucleotide 3 and nucleotide 4 of the target gene, whereby integration of the editing element at the target locus results in the target locus comprising an HBB coding sequence or stuffer-inserted coding sequence starting with the start codon of the target gene.
- 30 79. The AAV of any one of claims 73-77, wherein the editing element comprises an HBB coding sequence or stuffer-inserted coding sequence consisting of 5' to 3' a start codon and the nucleotide sequence encoding SEQ ID NO: 48, or a portion of the HBB coding sequence or stuffer-inserted coding sequence.

80. The AAV of claim 79, wherein the target locus is in an intron of the target gene, and wherein the editing element comprises 5' to 3' a splice acceptor site, a ribosomal skipping element, and an HBB coding sequence or stuffer-inserted coding sequence.
- 5 81. The AAV of claim 80, wherein the target locus is in intron 1 of the HBB gene.
82. The AAV of claim 79, wherein the target locus is adjacently 3' to a coding nucleotide of the target gene, and wherein the editing element comprises 5' to 3' a ribosomal skipping element and an HBB coding sequence or stuffer-inserted coding sequence.
- 10 83. The AAV of claim 82, wherein the target locus is the stop codon of a wild-type target gene or the corresponding nucleotides of a mutant target gene.
84. The AAV of any one of claims 73-83, wherein the editing element further comprises
15 an exogenous polyadenylation sequence 3' to the nucleotide sequence encoding SEQ ID NO: 48.
85. The AAV of any one of claims 63-84, wherein the editing element further comprises a
20 restriction endonuclease site not present in the target gene.
86. The AAV of any one of claims 63-85, wherein the editing element comprises the
nucleotide sequence set forth in any one of SEQ ID NOs: 23-28.
87. The AAV of any one of claims 63-86, wherein the 5' homology arm nucleotide
25 sequence is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the first genomic region.
88. The AAV of any one of claims 63-87, wherein the 3' homology arm nucleotide
sequence is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the second genomic
30 region.
89. The AAV of any one of claims 62-88, wherein the first genomic region is located in a
first editing window, and the second genomic region is located in a second editing window.
90. The AAV of claim 89, wherein the first and second editing windows are different.

91. The AAV of claim 89, wherein the first and second editing windows are the same.
92. The AAV of any one of claims 89-91, wherein the first editing window consists of the
5 nucleotide sequence set forth in SEQ ID NO: 101, 102, or 103.
93. The AAV of any one of claims 89-92, wherein the second editing window consists of the nucleotide sequence set forth in SEQ ID NO: 101, 102, or 103.
- 10 94. The AAV of any one of claims 89-93, wherein the first genomic region consists of the nucleotide sequence set forth in SEQ ID NO: 101.
95. The AAV of any one of claims 89-94, wherein the second genomic region consists of the nucleotide sequence set forth in SEQ ID NO: 102.
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96. The AAV of any one of claims 63-95, wherein the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 101.
97. The AAV of any one of claims 63-96, wherein the 3' homology arm consists of the
20 nucleotide sequence set forth in SEQ ID NO: 102.
98. The AAV of any one of the claims 63-97, wherein each of the 5' and 3' homology arm nucleotide sequences independently has a length of about 100 to about 2000 nucleotides.
- 25 99. The AAV of any one of the claims 63-98, wherein the correction genome further comprises a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the 5' homology arm nucleotide sequence, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the 3' homology arm nucleotide sequence.
- 30 100. The AAV of claim 99, wherein the 5' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:18, and the 3' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:19.

101. The AAV of claim 99, wherein the 5' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:20, and the 3' ITR nucleotide sequence has at least 95% sequence identity to SEQ ID NO:21.

5 102. The AAV of any one of claims 63-101, wherein the correction genome comprises the nucleotide sequence set forth in any one of SEQ ID NOs: 29-42 and 104.

103. The AAV of any one of claims 63-102, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid
10 sequence of amino acids 203-736 of SEQ ID NO:2, wherein: the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid
15 protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid
20 protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in
25 the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.

104. The AAV of claim 103, wherein:

- (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO:
30 2 is G;
- (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is

R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;

(c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO:

5 2 is R;

(d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or

(e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.

105. The AAV of claim 103, wherein the capsid protein comprises the amino acid
15 sequence of amino acids 203-736 of SEQ ID NO: 2, 3, 4, 6, 7, 10, 11, 12, 13, 15, 16, or 17.

106. The AAV of any one of claims 63-105, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of amino acids 138-736 of SEQ ID NO:2, wherein: the amino acid in the capsid
20 protein corresponding to amino acid 151 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 2 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid
25 protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid
30 protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the

capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.

107. The AAV of claim 106, wherein:

- 5 (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G;
- (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;
- 10 (c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R;
- 15 (d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or
- (e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.
- 20

108. The AAV of claim 106, wherein the capsid protein comprises the amino acid sequence of amino acids 138-736 of SEQ ID NO: 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17.

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109. The AAV of any one of claims 63-108, wherein the AAV Clade F capsid protein comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of amino acids 1-736 of SEQ ID NO: 2, wherein: the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 2 is T; the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 68 of SEQ ID NO: 2 is V; the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 2 is R; the amino acid in the capsid

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- protein corresponding to amino acid 119 of SEQ ID NO: 2 is L; the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 2 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 2 is C; the amino acid in the capsid
- 5 protein corresponding to amino acid 296 of SEQ ID NO: 2 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S; the amino acid in the capsid
- 10 protein corresponding to amino acid 501 of SEQ ID NO: 2 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M; the amino acid in the
- 15 capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G.
- 20 110. The AAV of claim 109, wherein:
- (a) the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 2 is T, and the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 2 is Q;
- (b) the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 2 is I, and the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is Y;
- 25 (c) the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 2 is K;
- 30 (d) the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 2 is L, and the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 2 is S;

- (e) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 2 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 2 is G;
- (f) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 2 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 2 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 2 is M;
- (g) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 2 is R;
- (h) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 2 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R; or
- (i) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 2 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 2 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 2 is C.
111. The AAV of claim 109, wherein the capsid protein comprises the amino acid sequence of amino acids 1-736 of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.
112. The AAV of any one of claims 63-111, wherein the integration efficiency of the editing element into the target locus is at least 1% when the AAV is contacted *in vitro* in the absence of an exogenous nuclease with a population of CD34⁺ human stem cells under standard AAV transduction conditions.
113. The AAV of any one of claims 63-112, wherein the allelic frequency of integration of the editing element into the target locus is at least 0.5% when the AAV is contacted *in vitro* in the absence of an exogenous nuclease with a population of CD34⁺ human stem cells under standard AAV transduction conditions.
114. A pharmaceutical composition comprising an AAV of any one of the claims 62-111.

115. A packaging system for recombinant preparation of an AAV, wherein the packaging system comprises
- a) a Rep nucleotide sequence encoding one or more AAV Rep proteins;
 - 5 b) a Cap nucleotide sequence encoding one or more AAV Clade F capsid proteins as set forth in any one of claims 103-111; and
 - c) a correction genome as set forth in any one of claims 63-102, wherein the packaging system is operative in a cell for enclosing the correction genome in the capsid to form the AAV.
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116. The packaging system of claim 115, wherein the packaging system comprises a first vector comprising the Rep nucleotide sequence and the Cap nucleotide sequence, and a second vector comprising the correction genome.
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117. The packaging system of 115 or 116, wherein the Rep nucleotide sequence encodes an AAV2 Rep protein.
118. The packaging system of claim 117, wherein the AAV2 Rep protein is 78/68 or Rep 68/52.
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119. The packaging system of claim 117 or 118, wherein the AAV2 Rep protein comprises an amino acid sequence having a minimum percent sequence identity to the AAV2 Rep amino acid sequence of SEQ ID NO:22, wherein the minimum percent sequence identity is at least 70% across the length of the amino acid sequence encoding the AAV2 Rep protein.
- 25
120. The packaging system of any one of claims 115-119, further comprising a third vector, wherein the third vector is a helper virus vector.
121. The packaging system of claim 120, wherein the helper virus vector is an independent
- 30 third vector.
122. The packaging system of claim 120, wherein the helper virus vector is integral with the first vector.

123. The packaging system of claim 120, wherein the helper virus vector is integral with the second vector.

124. The packaging system of any one of claims 120-123, wherein the third vector
5 comprises genes encoding helper virus proteins.

125. The packaging system of any one of claims 120-124 wherein the helper virus is selected from the group consisting of adenovirus, herpes virus, vaccinia virus, and cytomegalovirus (CMV).
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126. The packaging system of claim 125, wherein the helper virus is adenovirus.

127. The packaging system of claim 126, wherein the adenovirus genome comprises one or more adenovirus RNA genes selected from the group consisting of E1, E2, E4 and VA.
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128. The packaging system of claim 125, wherein the helper virus is herpes simplex virus (HSV).

129. The packaging system of claim 128, wherein the HSV genome comprises one or more
20 of HSV genes selected from the group consisting of UL5/8/52, ICPO, ICP4, ICP22 and UL30/UL42.

130. The packaging system of any one of claims 120-129, wherein the first vector and the third vector are contained within a first transfecting plasmid.
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131. The packaging system of any one of claims 120-129, wherein the nucleotides of the second vector and the third vector are contained within a second transfecting plasmid.

132. The packaging system of any one of claims 120-129, wherein the nucleotides of the
30 first vector and the third vector are cloned into a recombinant helper virus.

133. The packaging system of any one of claims 120-129, wherein the nucleotides of the second vector and the third vector are cloned into a recombinant helper virus.

134. A method for recombinant preparation of an AAV, the method comprising introducing the packaging system of any one of claims 115-133 into a cell under conditions operative for enclosing the correction genome in the capsid to form the AAV.