CLAIMS

1. A method for editing a hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter in a cell, the method comprising contacting the cell with a guide RNA and a fusion protein comprising a polynucleotide programmable DNA binding domain and an adenosine deaminase domain, wherein the adenosine deaminase domain comprises an arginine (R) or a threonine (T) at amino acid position 147 of SEQ ID NO: 2, wherein the adenosine deaminase domain has at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 2, wherein said guide RNA targets said fusion protein to effect a deamination of a nucleobase of the HBG1/2 promoter in the cell.

2. The method of claim 1, wherein the adenosine deaminase domain comprises an arginine (R) at amino acid position 147 of said amino acid sequence.

3. The method of claim 1, wherein the adenosine deaminase domain further comprises one or more of the following alterations: Q154S, Y123H, and Q154R.

4. The method of claim 1, wherein the adenosine deaminase domain comprises a combination of alterations selected from the group consisting of:

Y147T and Q154R;
Y147T and Q154S;
Y147R and Q154S;
Y147R, V82S and Q154S;
Y147T, V82S and Q154S;
V82S and Y147R;
Y147R, V82S and Q154R;
Y147T, V82S and Q154R;
Y147R, V82S and Y123H;
Y147T, V82S and Y123H;
Y147R, I76Y and V82S;
Y147T, I76Y and V82S;
V82S, Y123H, and Y147T;

V82S, Y123H, and Y147R;
Y147R, V82S, Y123H, and Q154R;
Y147T, V82S, Y123H, and Q154R;
Y147R, Q154R, and Y123H;
Y147R, Q154R, and I76Y;
Y147R, Q154R, and T166R;
Y123H, Y147R, Q154R, and I76Y;
V82S, Y123H, Y147R, and Q154R; and
I76Y, V82S, Y123H, Y147R, and Q154R.

5. The method of claim 1, wherein the adenosine deaminase domain comprises Y147R, Q154R, and Y123H.

6. The method of claim 1, wherein the fusion protein comprises a heterodimer comprising a wild-type adenosine deaminase domain and the adenosine deaminase domain of claim 1.

7. The method of claim 1, wherein deamination of the nucleobase creates a poly-G stretch of 10-nt in the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter.

8. The method of claim 1, wherein deamination of the nucleobase disrupts repressor binding to the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter.

9. The method of claim 1, wherein deamination of the nucleobase effects an increase in gamma globin expression.

10. The method of claim 1, wherein the polynucleotide programmable DNA binding domain comprises a Cas9 domain.

11. The method of claim 10, wherein the Cas9 domain comprises a dead Cas9 (dCas9) or a nickase Cas9 (nCas9).

12. The method of claim 11, wherein the Cas9 domain is capable of programable DNA binding and is selected from the group consisting of a *Streptococcus pyogenes* Cas9 (SpCas9), *Staphylococcus aureus* Cas9 (SaCas9), and a *Streptococcus thermophilus 1* Cas9 (St1Cas9).

13. The method of claim 11, wherein the Cas9 domain comprises an amino acid sequence having at least 85% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 1.

14. The method of claim 1 wherein the adenosine deaminase domain comprises a truncated TadA8 comprising a deletion of 1, 2, 3, 4, 5, 6, 7, or 8 N-terminal or C-terminal amino acid residues relative to a full length TadA8 comprising the amino acid sequence of SEQ ID NO: 17.

15. The method of claim 1, wherein the polynucleotide programmable DNA binding domain comprises the amino acid sequence of SEQ ID NO: 3.

16. A method of producing a red blood cell, or progenitor thereof, comprising:

(a) introducing into a red blood cell progenitor:

(i) a fusion protein, or a polynucleotide encoding said fusion protein, wherein said fusion protein comprises the fusion protein of claim 1, and

(ii) one or more guide polynucleotides, wherein said one or more guide polynucleotides target said fusion protein to effect an A•T to G•C alteration of a nucleobase of the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter region; and

(b) differentiating the red blood cell progenitor into a red blood cell.

17. A method for editing a hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter in a cell, the method comprising contacting the cell with a guide RNA and a fusion protein comprising a polynucleotide programmable DNA binding domain and an adenosine deaminase domain, wherein the adenosine deaminase domain comprises an arginine (R) or a threonine (T) at amino acid position 147 of SEQ ID NO: 2, wherein the adenosine deaminase domain has at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 2, wherein said guide RNA targets said fusion protein to effect a deamination of a nucleobase of the HBG1/2 promoter in the cell, wherein the method comprises introducing a A•T to G•C alteration at position -198 of the HBG1/2 promoter.

18. The method of claim 17, wherein the adenosine deaminase domain comprises an arginine (R) at amino acid position 147 of said amino acid sequence.

19. The method of claim 17, wherein the adenosine deaminase domain further comprises one or more of the following alterations: Q154S, Y123H, and Q154R.

20. The method of claim 17, wherein the adenosine deaminase domain comprises a combination of alterations selected from the group consisting of:

Y147T and Q154R;
Y147T and Q154S;
Y147R and Q154S;
Y147R, V82S and Q154S;
Y147T, V82S and Q154S;
V82S and Y147R;
Y147R, V82S and Q154R;
Y147T, V82S and Q154R;
Y147R, V82S and Y123H;
Y147T, V82S and Y123H;
Y147R, I76Y and V82S;
Y147T, I76Y and V82S;
V82S, Y123H, and Y147T;
V82S, Y123H, and Y147R;
Y147R, V82S, Y123H, and Q154R;
Y147T, V82S, Y123H, and Q154R;
Y147R, Q154R, and Y123H;
Y147R, Q154R, and I76Y;
Y147R, Q154R, and T166R;
Y123H, Y147R, Q154R, and I76Y;
V82S, Y123H, Y147R, and Q154R; and
I76Y, V82S, Y123H, Y147R, and Q154R.

21. The method of claim 17, wherein the adenosine deaminase domain comprises Y147R, Q154R, and Y123H.

22. The method of claim 17, wherein the fusion protein comprises a heterodimer comprising a wild-type adenosine deaminase domain and the adenosine deaminase domain of claim 17.

23. The method of claim 17, wherein deamination of the nucleobase creates a poly-G stretch of 10-nt in the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter.

24. The method of claim 17, wherein deamination of the nucleobase disrupts repressor binding to the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter.

25. The method of claim 17, wherein deamination of the nucleobase effects an increase in gamma globin expression.

26. The method of claim 17, wherein the polynucleotide programmable DNA binding domain comprises a Cas9 domain.

27. The method of claim 26, wherein the Cas9 domain comprises a dead Cas9 (dCas9) or a nickase Cas9 (nCas9).

28. The method of claim 27, wherein the Cas9 domain is capable of programable DNA binding and is selected from the group consisting of a *Streptococcus pyogenes* Cas9 (SpCas9), *Staphylococcus aureus* Cas9 (SaCas9), and a *Streptococcus thermophilus 1* Cas9 (St1Cas9).

29. The method of claim 27, wherein the Cas9 domain comprises an amino acid sequence having at least 85% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 1.

30. The method of claim 17 wherein the adenosine deaminase domain comprises a truncated TadA8 comprising a deletion of 1, 2, 3, 4, 5, 6, 7, or 8 N-terminal or C-terminal amino acid residues relative to a full length TadA8 comprising the amino acid sequence of SEQ ID NO: 17.

31. The method of claim 17, wherein the polynucleotide programmable DNA binding domain comprises the amino acid sequence of SEQ ID NO: 3.

32. A method of producing a red blood cell, or progenitor thereof, comprising:

(a) introducing into a red blood cell progenitor:

(i) a fusion protein, or a polynucleotide encoding said fusion protein, wherein said fusion protein comprises the fusion protein of claim 17, and

(ii) one or more guide polynucleotides, wherein said one or more guide polynucleotides target said fusion protein to effect an A•T to G•C alteration of a nucleobase of the hemoglobin subunit gamma 1 and/or 2 (HBG1/2) promoter region; and

(b) differentiating the red blood cell progenitor into a red blood cell.