CLAIMS

1. An *ex vivo* or *in vitro* method for producing a hematopoietic progenitor cell having decreased BCL11A mRNA or protein expression, the method comprising introducing an RNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease or a vector encoding a DNA-targeting endonuclease into an isolated human hematopoietic progenitor cell, *ex vivo* or *in vitro,* whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the human hematopoietic progenitor cell at chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly), and causes at least one genetic modification in DNAse 1-hypersensitive site (DHS) +62, DHS +58, or DHS +55 therein, and thereby reduces the mRNA or protein expression of BCL11A in the human hematopoietic progenitor cell.

2. An *ex vivo* or *in vitro* method for producing an isolated genetically engineered human hematopoietic progenitor cell having at least one genetic modification comprising introducing into an isolated hematopoietic progenitor cell, *ex vivo* or *in vitro,* an effective amount of a composition comprising at least an RNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly), and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein.

3. A method according to Claim 1 or 2, in which the isolated human hematopoietic progenitor cell or its progeny is a cell of the erythroid lineage.

4. A method according to Claim 1 or 2, in which the isolated human hematopoietic progenitor cell is derived from an induced pluripotent stem cell.

5. A method according to any preceding claim, in which the at least one genetic modification is a deletion.

6. A method according to Claim 5, in which the deletion removes the entire region between chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome

Browser hg 19 human genome assembly) or removes a portion of the region resulting in disruption of one of more of the DHSs.

7. An isolated genetically engineered human hematopoietic progenitor cell having at least one genetic modification on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) according to any of Claims 2 to 6.

8. A composition comprising isolated genetically engineered human hematopoietic progenitor cells according to Claim 7.

9. An *ex vivo* or *in vitro* method of increasing fetal hemoglobin levels in a cell, the method comprising the steps of: introducing into an isolated human hematopoietic progenitor cell, *ex vivo* or *in vitro,* an effective amount of a composition comprising at least an RNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease, or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein, whereby fetal hemoglobin expression is increased in the isolated human hematopoietic progenitor cell, or its progeny, relative to the isolated human hematopoietic progenitor cell prior to the contacting.

10. A method according to Claim 9, in which the isolated human hematopoietic progenitor cell or its progeny is a cell of the erythroid lineage.

11. A method according to Claim 9 or 10, in which the isolated human hematopoietic progenitor cell is derived from an induced pluripotent stem cell.

12. A method according to Claim 9, 10 or 11, in which the at least one genetic modification is a deletion.

13. A method according to Claim 12, in which the deletion removes the entire region between chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) or removes a portion of the region resulting in disruption of one of more of the DHSs.

14. An isolated hematopoietic progenitor cell for use in increasing fetal hemoglobin levels in a human that has a β-hemoglobinopathy, in which the isolated human hematopoietic progenitor cell has been contacted *ex vivo* or *in vivo* with an effective amount of a composition comprising at least an RNA encoding a DNA-targeting endonuclease, a DNA targeting endonuclease, or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the isolated human hematopoietic progenitor cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein.

15. An isolated genetically engineered human hematopoietic progenitor cell according to Claim 7 or a composition according to Claim 8 for use in increasing fetal hemoglobin levels in a human that has a β-hemoglobinopathy.

16. A pharmaceutical composition for reducing the mRNA or protein expression of BCL11A in an isolated human hematopoietic progenitor cell and producing a human hematopoietic progenitor cell having decreased BCL11A mRNA or protein expression, comprising an RNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease, or a vector carrying the coding sequence of a DNA-targeting endonuclease, in which the DNA-targeting endonuclease that binds and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein.

17. A pharmaceutical composition for producing an isolated genetic engineered human hematopoietic progenitor cell having at least one genetic modification, comprising at least an RNA encoding a DNA-targeting endonuclease, a DNA targeting endonuclease, or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification DHS +62, DHS +58, or DHS +55 therein.

18. A pharmaceutical composition according to Claim 16 or 17 in which isolated the human hematopoietic progenitor cell is a cell of the erythroid lineage.

19. A pharmaceutical composition according to Claim 16 or 17, in which the isolated human hematopoietic progenitor cell is derived from an induced pluripotent stem cell.

20. A pharmaceutical composition according to Claim 17, 18 or 19, in which the at least one genetic modification is a deletion.

21. A pharmaceutical composition according to Claim 20, in which the deletion removes the entire region between chromosome 2 location 60,716,189-60,728,612 or removes a portion of the region resulting in disruption of one of more DHSs.

22. A pharmaceutical composition for increasing fetal hemoglobin levels in a cell, comprising at least an RNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease, or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein, in which an isolated human hematopoietic progenitor cell is contacted and whereby fetal hemoglobin expression is increased in the cell, or its progeny, relative to the cell prior to the contacting.

23. A pharmaceutical composition according to Claim 22, in which the isolated human hematopoietic progenitor cell or its progeny is a cell of the erythroid lineage.

24. A pharmaceutical composition according to Claim 22 or 23, in which the isolated human hematopoietic progenitor cell is derived from an induced pluripotent stem cell.

25. A pharmaceutical composition according to Claim 22, 23 or 24, in which the at least one genetic modification is a deletion.

26. A pharmaceutical composition according to Claim 25, in which the deletion removes the entire region between chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) or removes a portion of the region resulting in disruption of one of more DHSs.

27. A pharmaceutical composition comprising an isolated human hematopoietic progenitor cell for use in increasing fetal hemoglobin levels in a human that has a β-hemoglobinopathy, in which the isolated human hematopoietic progenitor cell has been contacted with an effective amount of a composition comprising at least an mRNA encoding a DNA-targeting endonuclease, a DNA-targeting endonuclease, or a vector encoding a DNA-targeting endonuclease whereby the DNA-targeting endonuclease binds to and cleaves the genomic DNA of the cell on chromosome 2 location 60,716,189-60,728,612 (according to UCSC Genome Browser hg 19 human genome assembly) and causes at least one genetic modification in DHS +62, DHS +58, or DHS +55 therein.

28. A pharmaceutical composition comprising an isolated genetically engineered human hematopoietic progenitor cell according to Claim 7 or a composition according to Claim 8 for increasing fetal hemoglobin levels in a human that has a β-hemoglobinopathy.