Claims:

1. A guide RNA (gRNA) molecule comprising, from 5’ to 3’, [targeting domain]-SEQ ID NO: 231, wherein the targeting domain comprises SEQ ID NO: 67.

2. The gRNA molecule of claim 1, wherein the targeting domain and said SEQ ID NO: 231 are disposed on a single nucleic acid molecule, wherein said single nucleic acid molecule comprises said targeting domain and said SEQ ID NO: 231 that is disposed immediately 3’ to said targeting domain.

3. The gRNA molecule of claim 1 or claim 2, consisting of, from 5’ to 3’, [targeting domain]-SEQ ID NO: 231, wherein the targeting domain comprises SEQ ID NO: 67.

4. The gRNA molecule of any one of claims 1-3, comprising:
(a) one, two, or three phosphorothioate modifications at the 3’ end of said gRNA molecule;
(b) one, two, or three phosphorothioate modifications at the 5’ end of said gRNA molecule;
(c) one, two, or three 2’-O-methyl modifications at the 3’ end of said gRNA molecule;
(d) one, two, or three 2’-O-methyl modifications at the 5’ end of said gRNA molecule;
(e) a 2’ O-methyl modification at each of the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 3’ residues of said gRNA molecule;
(f) a 2’ O-methyl modification at each of the 4th-to-terminal, 3rd-to-terminal, and 2nd-to-terminal 5’ residues of said gRNA molecule; or
(g) any combination thereof.

5. The gRNA molecule of claim 1, comprising the sequence of SEQ ID NO: 174, SEQ ID NO: 175, or SEQ ID NO: 176.

6. The gRNA molecule of claim 1, consisting of the sequence of SEQ ID NO: 174, SEQ ID NO: 175, or SEQ ID NO: 176.

7. The gRNA molecule of claim 1, consisting of the sequence of SEQ ID NO: 174.

8. The gRNA molecule of any one of claims 1-7, wherein:
(a) when a CRISPR system comprising the gRNA molecule is introduced into a cell, an indel is formed at or near a target sequence complementary to the targeting domain of the gRNA molecule; and/or
(b) when a CRISPR system comprising the gRNA molecule is introduced into a cell, a deletion is

created comprising a sequence between a sequence complementary to the gRNA targeting domain in the HBG1 promoter region and a sequence complementary to the gRNA targeting domain in the HBG2 promoter region.

9. A composition comprising:
(a) the gRNA molecule of any one of claims 1-8 and a Cas9 molecule;
(b) the gRNA molecule of any one of claims 1-8 and a nucleic acid encoding a Cas9 molecule;
(c) a nucleic acid encoding the gRNA molecule of any one of claims 1-8 and a Cas9 molecule;
(d) a nucleic acid encoding the gRNA molecule of any one of claims 1-8 and a nucleic acid encoding a Cas9 molecule; or
(e) any one of (a) to (d), above, and a template nucleic acid; or
(f) any one of (a) to (d) above, and a nucleic acid comprising a sequence encoding a template nucleic acid.

10. A composition comprising the gRNA molecule of any one of claims 1-8, further comprising a Cas9 molecule, wherein the Cas9 molecule comprises SEQ ID NO: 205 or a sequence with at least 95% sequence homology thereto.

11. The composition of claim 9 or claim 10, wherein the Cas9 molecule comprises the sequence of:
(a) SEQ ID NO: 233;
(b) SEQ ID NO: 234;
(c) SEQ ID NO: 235;
(d) SEQ ID NO: 236;
(e) SEQ ID NO: 237;
(f) SEQ ID NO: 238;
(g) SEQ ID NO: 239;
(h) SEQ ID NO: 240;
(i) SEQ ID NO: 241;
(j) SEQ ID NO: 242;
(k) SEQ ID NO: 243; or
(l) SEQ ID NO: 244.

12. The composition of any one of claims 9-11, wherein the gRNA molecule and the Cas9 molecule are present in a ribonuclear protein complex (RNP).

13. The composition of any one of claims 9-12, formulated in a medium suitable for

electroporation.

14. A nucleic acid sequence that encodes the gRNA molecule of any one of claims 1-8.

15. A vector comprising the nucleic acid of claim 14.

16. The vector of claim 15, wherein said vector is selected from the group consisting of a lentiviral vector, an adenoviral vector, an adeno-associated viral (AAV) vector, a herpes simplex virus (HSV) vector, a plasmid, a minicircle, a nanoplasmid, and an RNA vector.

17. An *ex-vivo* method of altering a cell at or near a target sequence within said cell, comprising contacting said cell with:
(a) the gRNA molecule of any one of claims 1-8 and a Cas9 molecule;
(b) the gRNA molecule of any one of claims 1-8 and a nucleic acid encoding a Cas9 molecule;
(c) a nucleic acid encoding the gRNA molecule of any one of claims 1-8 and a Cas9 molecule;
(d) a nucleic acid encoding the gRNA molecule of any one of claims 1-8 and a nucleic acid encoding a Cas9 molecule;
(e) any one of (a) to (d), above, and a template nucleic acid;
(f) any one of (a) to (d) above, and a nucleic acid comprising a sequence encoding a template nucleic acid;
(g) the composition of any one of claims 9-13; or
(h) the vector of claim 15.

18. An *ex-vivo* method of altering a cell at or near a target sequence within said cell, comprising contacting said cell with:
(a) a gRNA molecule comprising a tracr and crRNA, wherein the crRNA comprises a targeting domain that comprises SEQ ID NO: 67, or a nucleic acid encoding said gRNA molecule; and
(b) a Cas9 molecule, or a nucleic acid encoding said Cas9 molecule,
wherein the method results in a population of cells wherein at least about 15% of the population have been altered.

19. The *ex-vivo* method of claim 18, wherein the tracr comprises:
(a) SEQ ID NO: 73
(b) SEQ ID NO: 187;
(c) SEQ ID NO: 188;
(d) SEQ ID NO: 203;
(e) SEQ ID NO: 204;

(f) SEQ ID NO: 224;
(g) SEQ ID NO: 225;
(h) SEQ ID NO: 232;
(i) SEQ ID NO: 227;
(j) (SEQ ID NO: 228;
(k) SEQ ID NO: 229;
(l) any of (a) to (k), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 uracil (U) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 uracil (U) nucleotides;
(m) any of (a) to (l), above, further comprising, at the 3' end, at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides; or
(n) any of (a) to (m), above, further comprising, at the 5' end (e.g., at the 5' terminus), at least 1, 2, 3, 4, 5, 6 or 7 adenine (A) nucleotides, e.g., 1, 2, 3, 4, 5, 6, or 7 adenine (A) nucleotides.

20. The *ex-vivo* method of claim 19, wherein the tracr comprises:
(a) SEQ ID NO: 73;
(b) SEQ ID NO: 187;
(c) SEQ ID NO: 188; or
(b) SEQ ID NO: 224.

21. The *ex-vivo* method of claim 17, wherein the method results in a population of cells wherein at least about 15% of the population have been altered.

22. The *ex-vivo* method of any one of claims 17-21, wherein:
(a) the altering results in a cell that is capable of differentiating into a differentiated cell of an erythroid lineage, wherein said differentiated cell exhibits an increased level of fetal hemoglobin relative to a population of unaltered cells;
(b) the altering results in a population of cells that is capable of differentiating into a population of differentiated cells, wherein said population of differentiated cells has an increased percentage of F cells relative to a population of unaltered cells; and/or
(c) the altering results in a cell that is capable of differentiating into a differentiated cell, wherein said differentiated cell produces at least about 6 picograms fetal hemoglobin per cell.

23. A cell altered by the *ex-vivo* method of any one of claims 17-22, or a cell obtained by the *ex-vivo* method of any one of claims 17-22.

24. A cell comprising the gRNA molecule of any one of claims 1-8 and a Cas9 molecule.

25. A population of cells comprising the cell of claim 23 or claim 24, wherein at least about 50% of the cells of the population are a cell according to claim 23 or claim 24.

26. A composition comprising the cell of claim 23 or claim 24 or the population of cells of claim 25, and a pharmaceutically acceptable medium.

27. A method of preparing a cell, comprising:
(a) providing a cell;
(b) culturing said cell ex vivo in a cell culture medium comprising a stem cell expander; and
(c) introducing into said cell the gRNA molecule of any one of claims 1-8, a nucleic acid molecule encoding the gRNA molecule of any one of claims 1-8, the composition of any one of claims 9-13, the nucleic acid of claim 14, or the vector of claim 15.

28. The method of claim 27, wherein the stem cell expander is:
(a) (1r,4r)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine;
(b) methyl 4-(3-piperidin-1-ylpropylamino)-9H-pyrimido[4,5-b]indole-7-carboxylate;
(c) 4-(2-(2-(benzo[b]thiophen-3-yl)-9-isopropyl-9H-purin-6-ylamino)ethyl)phenol;
(d) (S)-2-(6-(2-(lH-indol-3-yl)ethylamino)-2-(5-fluoropyridin-3-yl)-9H-purin-9-yl)propan-l-ol; or
(e) combinations thereof.

29. The method of claim 27 or claim 28, wherein the cell culture medium comprises thrombopoietin (Tpo), Flt3 ligand (Flt-3L), and human stem cell factor (SCF), or additionally interleukin-6 (IL-6).

30. The method of any one of claims 27-29, wherein the introducing of step (c) comprises an electroporation.

31. A cell obtained by the method of any one of claims 27-30.

32. The gRNA molecule of claim 8, the method of any one of claims 17-22 and 27-30, the cell of any one of claims 23, 24, and 31, or the population of claim 25, wherein the cell is a hematopoietic stem or progenitor cell (HSPC).

33. The gRNA molecule of claim 8, the method of any one of claims 17-22 and 27-30, the cell of any one of claims 23, 24, and 31, the population of claim 25, wherein the cell has been isolated

from bone marrow, peripheral blood, or umbilical cord blood.

34. Use of the cell of any one of claims 23, 24, and 31-33, the population of any one of claims 25, 32, and 33, or the composition of claim 26 in the manufacture of a medicament for the treatment of hemoglobinopathy in a patient.

35. Use of the cell of any one of claims 23, 24, and 31-33, the population of any one of claims 25, 32, and 33, or the composition of claim 26 in the manufacture of a medicament for increasing fetal hemoglobin expression in a patient.

36. The use of claim 34 or claim 35, wherein the patient is to be administered at least about 2e6 cells of any one of claims 23, 24, and 31-33 per kg body weight of the patient.

37. The use of claim 34 or claim 36, wherein the hemoglobinopathy is sickle cell disease or beta-thalassemia.

38. The cell of any one of claims 23, 24, and 31-33, the population of any one of claims 25, 32, and 33, or the composition of claim 26, for use in therapy.