CLAIMS

1. An isolated polynucleotide encoding a homing endonuclease (HE), wherein said endonucleases binds to a nucleotide sequence selected from the group consisting of a Bcl 11a coding region, a Bcl 11a gene regulatory region, a fetal hemoglobin (HbF) silencing region, and a Bcl 11a-regulated HbF silencing region.

2. The isolated polynucleotide of claim 1, wherein the endonuclease is

a) a HE that binds to said Bcl 11a coding region or said Bcl 11a gene regulatory region; or

b) a HE that can specifically bind to a fetal hemoglobin (HbF) silencing region;

optionally wherein the HE is selected from the group consisting of an I-Onul homing endonuclease, an I-HjeMI homing endonuclease, and an I-CpaMI homing endonuclease.

3. The isolated polynucleotide of claim 1 or 2, wherein the endonuclease is an I-Onul homing endonuclease,

such as wherein the I-Onul homing endonuclease comprises the amino acid sequence encoded by a variant of the nucleotide sequence of SEQ ID NO: 34 that encodes an I-Onul homing endonuclease that can specifically bind to the fetal hemoglobin (HbF) silencing region;

optionally wherein the I-Onul homing endonuclease comprises one or more amino acid substitutions within the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 34, wherein each of the amino acid substitutions is selected from the group consisting of L26, R28, R30, N32, S40, E42, G44, Q46, A70, S72, S78, K80, and T82; or

optionally wherein the I-Onul homing endonuclease comprises one or more amino acid substitutions within the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 34, wherein said amino acid substitution is

selected from the group consisting of F182, N184, 1186, S190, K191, Q197, V199, S201, K225, K227, D236, V238, and T240.

4. The isolated polynucleotide of any one of claims 1-3, further comprising a polynucleotide encoding a TAL effector (TALE) DNA binding domain, and/or a TREX2 nuclease,

such as wherein the polynucleotide encoding the HE endonuclease is fused to a polynucleotide encoding the TAL effector (TALE) DNA binding domain or a TREX2 nuclease.

5. A vector system comprising a vector and a polynucleotide according to any one of claims 1 to 4.

6. The vector system of claim 5, wherein the vector is selected from the group consisting of an AAV6, a modified adenovirus vector, an integration-deficient lentiviral vector (IDLV), and an integration-deficient foamyviral vector (IDFV).

7. An isolated homing endonuclease (HE) encoded by a polynucleotide according to any one of claims 1 to 4.

8. A composition for the use in the treatment of a hemoglobinopathy, comprising:

a) a polynucleotide according to any one of claims 1 to 4:

b) a vector system according to claim 5 or claim 6; or

c) a HE endonuclease according to claim 7.

9. A cell comprising a polynucleotide according to any one of claims 1 to 4, a vector system according to claim 5 or claim 6, or an endonuclease according to claim 7.

10. The cell of claim 9, wherein the cell is:

a) a stem cell;

b) a stem cell selected from the group consisting of a hematopoietic stem cell (HSC), an induced pluripotent stem cell (iPSC), an embryonic stem (ES) cell, and an erythroid progenitor cell; or

c) a stem cell selected from the group consisting of a hematopoietic stem cell (HSC), an induced pluripotent stem cell (iPSC), and an erythroid progenitor cell.