

~~What is claimed is~~ Claims:

1. A method of producing a hematopoietic stem cell or progenitor thereof for the treatment of a hemoglobinopathy, hematologic cancer, or myeloproliferative disease, the method comprising:

(a) expressing in the hematopoietic stem cell or progenitor thereof a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase; and

(b) contacting the hematopoietic stem cell or progenitor thereof with a guide RNA that targets a nucleic acid molecule encoding a cell surface protein selected from the group consisting of CD117, CXCR4, CD135, CD90, CD45, and CD34, and introducing a mutation in the cell surface protein.

2. Use of a hematopoietic stem cell or progenitor thereof in the preparation of a medicament for the treatment of a hemoglobinopathy, hematologic cancer, or myeloproliferative disease, wherein the hematopoietic stem cell or progenitor thereof is produced according to the method comprising:

(a) expressing in the hematopoietic stem cell or progenitor thereof a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase; and

(b) contacting the hematopoietic stem cell or progenitor thereof with a guide RNA that targets a nucleic acid molecule encoding a cell surface protein selected from the group consisting of CD117, CXCR4, CD135, CD90, CD45, and CD34, and introducing a mutation in the cell surface protein.

~~2. A method of producing a hematopoietic stem cell or progenitor thereof for the treatment of a hemoglobinopathy, hematologic cancer, or myeloproliferative disease, the method comprising~~

~~(a) expressing in a hematopoietic stem cell or progenitor thereof comprising a CD117 protein a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;~~

~~(b) contacting the hematopoietic stem cell or progenitor with a guide RNA capable of targeting a polynucleotide encoding the cell surface protein, thereby producing a~~

~~hematopoietic stem cell or progenitor thereof for the treatment of a hemoglobinopathy, hematologic cancer, or myeloproliferative disease.~~

3. The method of claim 1 or the use of claim 2, wherein the hemoglobinopathy is selected from the group consisting of sickle cell anemia, sickle cell disease (SCD), thalassemia, hereditary persistence of fetal hemoglobin (HPFH), Fanconi anemia, aplastic anemia, and Wiskott-Aldrich syndrome;

~~4. The method of claim 1 or 2, wherein the hematologic cancer is selected from the group consisting of acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, diffuse large B-cell lymphoma, and non-Hodgkin's lymphoma; and~~

~~5. The method of claim 1 or 2, wherein the myeloproliferative disease is a myelodysplastic syndrome.~~

~~6.4.~~ A method of identifying a mutation that alters antibody binding to a cell surface protein, the method comprising

(a) expressing in a cell comprising a cell surface protein a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;

(b) contacting the cell with a guide RNA capable of targeting a nucleic acid molecule encoding the cell surface protein and introducing a mutation in the cell surface protein; and

(c) contacting the cell with an antibody that specifically binds a wild-type cell surface protein, but that exhibits reduced binding to the cell surface protein comprising the mutation, thereby identifying a mutation that alters antibody binding to the cell surface protein.

~~7. The method of claim 6, wherein the method further comprises assaying a biological activity of the cell.~~

~~8.5.~~ The method of claim 1 or ~~64~~, or the use of claim 2, wherein the cell surface protein is selected from the group consisting of CD117, CXCR4, CD135, CD90, CD45, and CD34; and/or wherein the cell is selected from a hematopoietic stem cell or a progenitor thereof, or a

common myeloid progenitor, proerythroblast, or erythroblast; optionally, wherein the cell is a mammalian or a human cell.

~~9. The method of claim 1 or 6, wherein the cell surface protein is CD117.~~

~~106.~~ The method or use of any one of claims 9-5, wherein the method further comprises contacting the cell with one or more additional guide RNAs that target a cell surface protein selected from the group consisting of CXCR4, CD135, CD90, CD45, and CD34.

~~11. The method of claim 6, wherein the cell is a hematopoietic stem cell or a progenitor thereof.~~

~~12. The method of any one of claims 1-11, wherein the mutation is a missense mutation.~~

~~13. The method of claim 12, wherein the missense mutation fails to alter the biological activity of the cell surface protein.~~

~~14.7.~~ A method of identifying a mutation that alters antibody binding to a cell surface protein, the method comprising

(a) expressing in a hematopoietic stem cell or progenitor thereof a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;

(b) contacting the cell with a guide RNA capable of targeting a nucleic acid molecule encoding a cell surface protein selected from the group consisting of CD117, CXCR4, CD135, CD90, CD45, CD34, and introducing a mutation in the cell surface protein; and

(c) contacting the cell with an antibody that specifically binds a wild-type cell surface protein, but that exhibits reduced binding to the cell surface protein comprising a mutation, thereby identifying a mutation that alters antibody binding to the cell surface protein.

~~15.8.~~ A method of base editing a gene encoding a cell surface protein expressed by a hematopoietic stem cell or a progenitor thereof, the method comprising

(a) expressing in a hematopoietic stem cell or a progenitor thereof comprising a CD117 protein a nucleobase editor polypeptide, wherein the nucleobase editor polypeptide comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;

and

(b) contacting the cell with a guide RNA capable of targeting a nucleic acid molecule encoding the CD117 protein, thereby base editing the gene encoding the cell surface protein.

~~16.9.~~ The method of any one of claims 1-~~15~~8, wherein the deaminase domain is an adenosine deaminase or a cytidine deaminase.

~~17.10.~~ The method of claim ~~16~~9, wherein the adenosine deaminase is a TadA*8 variant.

~~18.11.~~ The method of claim ~~16 or 17~~10, wherein the adenosine deaminase is TadA*8.1, TadA*8.2, TadA*8.3, TadA*8.4, TadA*8.5, TadA*8.6, TadA*8.7, TadA*8.8, TadA*8.9, TadA*8.10, TadA*8.11, TadA*8.12, TadA*8.13, TadA*8.14, TadA*8.15, TadA*8.16, TadA*8.17, TadA*8.18, TadA*8.19, TadA*8.20, TadA*8.21, TadA*8.22, TadA*8.23, or TadA*8.24.

~~19.12~~ The method or use of any one of claims 1-~~18~~11, wherein the deaminase is a monomer or heterodimer;

~~20.~~ ~~The method of any one of claims 1-10,~~ wherein the nucleobase editor polypeptide is an internal base editor (IBE) comprising the deaminase domain inserted at an internal location of the napDNAbp;

~~21.~~ ~~The method of any one of claims 1-20,~~ wherein the nucleobase editor polypeptide further comprises one or more uracil glycosylase inhibitors (UGIs); and/or

~~22.~~ ~~The method of any one of claims 1-21,~~ wherein the nucleobase editor polypeptide further comprises one or more nuclear localization sequences (NLS).

~~23.13.~~ Use of a hematopoietic stem cell in the preparation of a medicament for ~~A method of~~ conditioning a subject concurrent with or subsequent to a hematopoietic stem cell transplant (HSCT), wherein the hematopoietic stem cell is prepared according to the method comprising

(a) expressing in an isolated hematopoietic stem cell of the subject or of a donor a nucleobase editor polypeptide comprising a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;

(b) contacting the hematopoietic stem cell with a guide RNA capable of targeting a nucleic acid molecule encoding a cell surface protein selected from the group consisting of CD117, CXCR4, CD135, CD90, CD45, and CD34, thereby introducing a mutation in the cell surface protein and generating an edited hematopoietic stem cell;

and wherein

(c) ~~administering~~ the edited hematopoietic stem cell is to be administered to the subject; and

(d) ~~administering to the subject~~ an antibody, antibody drug conjugate, or chimeric antigen receptor expressing T cell (CAR-T) that selectively binds a wild-type version of the cell surface protein, is to be administered to the subject, wherein the ~~administering of~~ administration step (d) is concurrent with or subsequent to the administration step (c).

1424. Use of a hematopoietic stem cell in the preparation of a medicament for ~~A method of~~ conditioning a subject concurrent with or subsequent to a hematopoietic stem cell transplant (HSCT), wherein the hematopoietic stem cell is prepared according to the method comprising

(a) expressing in a hematopoietic stem cell of the subject a nucleobase editor polypeptide comprising a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase;

(b) contacting the hematopoietic stem cell with a guide RNA capable of targeting a nucleic acid molecule encoding a CD117 protein, thereby introducing a mutation in the CD117 protein and generating an edited hematopoietic stem cell;

and wherein

(c) ~~administering~~ the edited hematopoietic stem cell is to be administered to the subject; and

(d) ~~administering to the subject~~ an antibody, antibody drug conjugate, or chimeric antigen receptor expressing T cell (CAR-T) that selectively binds a wild-type version of CD117, is to be administered to the subject, wherein the administration ~~administering of~~ step (d) is concurrent with or subsequent to administration step (c).

1525. The method-use of any one of claims 23 or 24~~claim 13 or 14~~, wherein the deaminase ~~domain~~ is an adenosine deaminase or a cytidine deaminase.

1626. The method-use of claim 25~~15~~, wherein the adenosine deaminase a TadA*8 variant.

~~1727.~~ The ~~method-use~~ of claim ~~25 or 26~~ 16, wherein the adenosine deaminase is TadA*8.1, TadA*8.2, TadA*8.3, TadA*8.4, TadA*8.5, TadA*8.6, TadA*8.7, TadA*8.8, TadA*8.9, TadA*8.10, TadA*8.11, TadA*8.12, TadA*8.13, TadA*8.14, TadA*8.15, TadA*8.16, TadA*8.17, TadA*8.18, TadA*8.19, TadA*8.20, TadA*8.21, TadA*8.22, TadA*8.23, or TadA*8.24.

~~2818.~~ The ~~method-use~~ of any one of claims ~~24-27~~ 13-17, wherein the deaminase is a monomer or heterodimer_;

~~29.~~ ~~The method of claim 23 or 24,~~ wherein the nucleobase editor polypeptide is an internal base editor (IBE) comprising the deaminase domain inserted at an internal location of the napDNAbp_;

~~30.~~ ~~The method of claim 23 or 24,~~ wherein the nucleobase editor polypeptide further comprises one or more uracil glycosylase inhibitors (UGIs)_;

~~31.~~ ~~The method of any one of claims 23-30,~~ wherein the nucleobase editor polypeptide further comprises one or more nuclear localization sequences (NLS)_; and/or

~~32.~~ ~~The method of any one of claims 23-30,~~ wherein the mutation is a missense mutation_; optionally,

~~33.~~ ~~The method of claim 32,~~ wherein the missense mutation fails to alter the biological activity of the cell surface protein.

~~1934.~~ The method or use of any one of claims 1-~~33~~ 18, wherein the CD117 cell surface protein comprising the mutation is capable of binding Stem Cell Factor (SCF)_; or is capable of SCF signaling.

~~35.~~ ~~The method of any one of claims 14-16,~~ wherein the CD117 cell surface protein comprising the mutation is capable of SCF signaling.

~~2036.~~ The method or use of any one of claims 1-~~35~~ 19, wherein the mutation is at least one amino acid substitution resulting from the modification of one or more single target

nucleobases.

2137. The method or use of claim 3620, wherein the single target nucleobase is a cytosine (C) and wherein the modification comprises conversion of the C to a thymine (T); or

~~38. The method of claim 36, wherein the single target nucleobase is an adenosine (A) and wherein the modification comprises conversion of the A to a guanine (G).~~

~~39. The method of any one of claims 36-38, wherein the at least one amino acid substitution is a naturally occurring mutation.~~

~~40. The method of any one of claims 36-38, wherein the at least one amino acid substitution is in domain 1, 2, 3, 4, or 5 of CD117.~~

2241. The method or use of ~~any one of claims 36-38~~ claim 20 or 21, wherein the at least one amino acid substitution in CD117 is selected from the group consisting of: ~~In some embodiments, the at least one amino acid substitution in CD117 is selected from the group of:~~ T13A, I39V, H40R, D45G, D52G, E53G, I54V, R55G, T59A, K65E, K65R, T67A, E76G, N77G, N77S, N77Y, K78E, Q79R, N80G, E81G, E81D, N99G, K100G, H101R, L124P, Y125H, D129E, D129G, N130D, N130G, D131G, D131N, T132A, T144A, N145D, N145G, N145Y, N145S, Y146C, F162P, F162L, I163T, I163V, M171T, I172T, V195A, L196P, K199G, I201V, S220G, Y221C, Q256R, E257D, E257G, K258E, Y259C, T303A, T304A, M318V, T322A, V323A, F324L, K342G, K342R, Y350H, M351T, R353G, T354A, T354I, R381G, K383G, T385A, Y418C, D419G, R420G, I438M, D439G, Q460R, T461A, K484G, N486G, and T488A.

~~42. The method of any one of claims 36-38, the at least one amino acid substitution in CD117 is a naturally occurring mutation selected from the group consisting of: T13A, N77S, D129E, N130D, D131N, T144A, Y221C, E257D, T322A, T354I, D419G.~~

~~43. The method of claim 6, wherein the is a hematopoietic stem cell, a common myeloid progenitor, proerythroblast, or erythroblast.~~

2344. The method or use of any one of claims 1-~~43~~ 22, wherein the cell is a CD34+ cell;

and/or

45. ~~The method of any one of claims 1-44,~~ wherein the cell is from a subject having hemoglobinopathy, hematologic cancer, or a myeloproliferative disease.

~~2446.~~ The method or use of claim ~~45~~23, wherein the cell is from a subject having sickle cell disease (SCD); or

47. ~~The method of claim 45,~~ wherein the cell is from a subject having hereditary persistence of fetal hemoglobin (HPFH).

48. ~~The method of any one of claims 1-47, wherein the cell is a mammalian cell.~~

49. ~~The method of claim 48, wherein the cell is a human cell.~~

~~2550.~~ The method or use of any one of claims 1-~~49~~24, wherein the deaminase domain is fused to the napDNAbp₁

51. ~~The method of any one of claims 1-49,~~ wherein the deaminase domain is inserted at an internal location of the napDNAbp₁

52. ~~The method of any one of 1-49,~~ wherein the napDNAbp is a nuclease inactive or nickase variant₁

53. ~~The method of any one of claims 1-49,~~ wherein the napDNAbp comprises a Cas9, Cas12a/Cpf1, Cas12b/C2c1, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, or Cas12j/CasΦ polynucleotide or a portion thereof₁

54. ~~The method of claim 53, wherein the napDNAbp comprises a Cas9 polynucleotide or a portion thereof.~~

55. ~~The method of any one of claims 1-54,~~ wherein the napDNAbp comprises a dead Cas9 (dCas9) or a Cas9 nickase (nCas9)₁

~~56.—The method of any one of claims 1-55, wherein the napDNAbp is a modified Staphylococcus aureus Cas9 (SaCas9), Streptococcus thermophilus 1 Cas9 (St1Cas9), a modified Streptococcus pyogenes Cas9 (SpCas9), or variants thereof; or~~

~~57.—The method of claim 55, wherein the napDNAbp comprises a variant of SpCas9 having an altered protospacer-adjacent motif (PAM) specificity; optionally,~~

~~58.—The method of claim 57, wherein the altered PAM has specificity for the nucleic acid sequence 5'-NGC-3';~~

~~59.—The method of any one of claims 1-57, wherein the deaminase domain is capable of deaminating cytidine or adenine in DNA.~~

~~2660. The method-use of any one of claims 23-59~~13-25, wherein the deaminase domain is a cytidine deaminase domain or an adenosine deaminase domain.

~~2761. The method-use of claim 59~~26, wherein the cytidine deaminase domain is an APOBEC deaminase domain or a derivative thereof; or

~~62.—The method of any one of claims 23-60, wherein the deaminase domain is an adenosine deaminase domain.~~

~~63.—The method of claim 61, wherein the adenosine deaminase domain is a TadA deaminase domain;~~

~~64.—The method of claim 61, wherein the adenosine deaminase is a TadA*8 variant; or~~

~~65.—The method of claim 64, wherein the adenosine deaminase is TadA*8.1, TadA*8.2, TadA*8.3, TadA*8.4, TadA*8.5, TadA*8.6, TadA*8.7, TadA*8.8, TadA*8.9, TadA*8.10, TadA*8.11, TadA*8.12, TadA*8.13, TadA*8.14, TadA*8.15, TadA*8.16, TadA*8.17, TadA*8.18, TadA*8.19, TadA*8.20, TadA*8.21, TadA*8.22, TadA*8.23, or TadA*8.24.~~

~~66.—The method of any one of claims 1-65, wherein the guide polynucleotide comprises a nucleic acid sequence comprising at least 10 contiguous nucleotides that are complementary~~

~~to a CD117 nucleic acid sequence.~~

~~2867.~~ The method or use of any one of claims 1-~~66~~27, wherein the one or more guide polynucleotides comprises a nucleic acid sequence selected from Table 23.

~~2968.~~ The method or use of any one of claims 1-~~67~~28, wherein the one or more guide polynucleotides comprise a nucleic acid sequence that hybridizes to the complement of a CD117 target sequence selected from the group consisting of:

CAAGCTATCTTCTTAGGGA;
GCAAGCTATCTTCTTAGGGAA;
ACTTACGACAGGCTCGTGAA;
TGACCAATTATTCCCTCAAG;
AGTGACCAATTATTCCCTCA;
ACTACAGTATTTGTAAACGA;
AAGACAACGACACGCTGGTC; and
GGCTGTTATGCACTGATCCG.

~~69.~~—The method of any one of claims 1-68, wherein the antibody is an anti-CD117 antibody.

~~70.~~—The method of any one of claims 1-68, wherein the antibody binds domain 1, 2, 3, 4, or 5 of CD117.

~~71.~~—The method of any one of claims 1-70, wherein the antibody is a monoclonal antibody.

~~72.~~—The method of claim 1 or 2, wherein the hemoglobinopathy is sickle cell disease (SCD).

~~73.~~—The method of claim 1 or 2, wherein the hemoglobinopathy is hereditary persistence of fetal hemoglobin (HPFH).

~~74.~~—The method of claim 72, wherein the sickle cell disease is associated with a mutation in a beta globin (HBB) polynucleotide.

~~75. The method of claim 73, wherein the HPFH is associated with a mutation in a Hemoglobin Subunit Gamma 1 (HBG1) and/or Hemoglobin Subunit Gamma 2 (HBG2) polynucleotide.~~

3076. A base editor system comprising a fusion protein or a polynucleotide encoding the fusion protein, wherein the fusion protein comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase domain, and a guide polynucleotide comprising a nucleic acid sequence selected from Table 23; or

~~77. A base editor system comprising a fusion protein or a polynucleotide encoding the fusion protein, wherein the fusion protein comprises a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase domain, and a guide polynucleotide comprising a nucleic acid sequence that hybridizes to the complement of a target nucleic acid sequence selected from the group consisting of:~~

CAAGCTATCTTCTTAGGGA;
GCAAGCTATCTTCTTAGGGAA;
ACTTACGACAGGCTCGTGAA;
TGACCAATTATTCCCTCAAG;
AGTGACCAATTATTCCCTCA;
ACTACAGTATTTGTAAACGA;
AAGACAACGACACGCTGGTC; and
GGCTGTTATGCACTGATCCG.

3178. The base editor system of claim ~~76 or 77~~30, wherein the fusion protein further comprises one or more uracil glycosylase inhibitors (UGIs); and/or

~~79. The base editor system of claim 76 or 77, wherein the fusion protein further comprises one or more nuclear localization sequences (NLS).~~

3280. The base editor system of any one of claims ~~76-79~~30 or 31, wherein the base editor system is capable of modifying one or more single target nucleobases to effect at least one amino acid substitution in a CD117 polypeptide.

3381. The base editor system of claim ~~80~~32, wherein the single target nucleobase is a

cytosine (C) and wherein the modification comprises conversion of the C to a thymine (T);
or

~~82. The base editor system of claim 80, wherein the single target nucleobase is an~~
adenosine (A) and wherein the modification comprises conversion of the A to a guanine (G).

~~83. The base editor system of claim 80, wherein the at least one amino acid substitution is~~
~~a naturally occurring mutation.~~

~~3484. The base editor system of claim 8333, wherein the at least one amino acid substitution~~
is in domain 1, 2, 3, 4, or 5 of CD117; or

~~85. The base editor system of claim 84, wherein the at least one amino acid substitution is~~
selected from the group consisting of: ~~In some embodiments, the at least one amino acid~~
~~substitution in CD117 is selected from the group of:~~ T13A, I39V, H40R, D45G, D52G,
E53G, I54V, R55G, T59A, K65E, K65R, T67A, E76G, N77G, N77S, N77Y, K78E, Q79R,
N80G, E81G, E81D, N99G, K100G, H101R, L124P, Y125H, D129E, D129G, N130D,
N130G, D131G, D131N, T132A, T144A, N145D, N145G, N145Y, N145S, Y146C, F162P,
F162L, I163T, I163V, M171T, I172T, V195A, L196P, K199G, I201V, S220G, Y221C,
Q256R, E257D, E257G, K258E, Y259C, T303A, T304A, M318V, T322A, V323A, F324L,
K342G, K342R, Y350H, M351T, R353G, T354A, T354I, R381G, K383G, T385A, Y418C,
D419G, R420G, I438M, D439G, Q460R, T461A, K484G, N486G, and T488A.

~~86. The base editor system of claim 85, wherein the at least one amino acid substitution is~~
~~a naturally occurring mutation selected from the group consisting of: T13A, N77S, D129E,~~
~~N130D, D131N, T144A, Y221C, E257D, T322A, T354I, D419G~~

~~3587. The base editor system of any one of claims 76-8630-34, wherein the napDNAbp is a~~
nuclease inactive or nickase variant;

~~88. The base editor system of any one of claims 76-86, wherein the napDNAbp comprises~~
a Cas9, Cas12a/Cpf1, Cas12b/C2c1, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g,
Cas12h, Cas12i, or Cas12j/CasΦ polynucleotide or a portion thereof;

~~89. The base editor system of any one of claims 76-86, wherein the napDNAbp comprises a Cas9 polynucleotide or a portion thereof;~~

~~90. The base editor system of any one of claims 76-89, wherein the napDNAbp comprises a dead Cas9 (dCas9) or a Cas9 nickase (nCas9);~~

~~91. The base editor system of any one of claims 76-90, wherein the napDNAbp is a modified Staphylococcus aureus Cas9 (SaCas9), Streptococcus thermophilus 1 Cas9 (St1Cas9), a modified Streptococcus pyogenes Cas9 (SpCas9), or variants thereof; or~~

~~92. The base editor system of claim 91, wherein the napDNAbp comprises a variant of SpCas9 having an altered protospacer-adjacent motif (PAM) specificity; optionally,~~

~~93. The base editor system of claim 92, wherein the altered PAM has specificity for the nucleic acid sequence 5'-NGC-3'.~~

~~3694. The base editor system of any one of claims 76-93~~30-35, wherein the deaminase domain is capable of deaminating cytidine or adenine in DNA;

~~95. The base editor system of any one of claims 76-94, wherein the deaminase domain is a cytidine deaminase domain;~~

~~96. The base editor system of claim 95, wherein the cytidine deaminase is an APOBEC deaminase or a derivative thereof;~~

~~97. The base editor system of claim 94, wherein the deaminase domain is an adenosine deaminase domain;~~

~~98. The base editor system of claim 97, wherein the adenosine deaminase is a TadA*8 variant;~~

~~99. The base editor system of claim 97 or 98, wherein the adenosine deaminase is TadA*8.1, TadA*8.2, TadA*8.3, TadA*8.4, TadA*8.5, TadA*8.6, TadA*8.7, TadA*8.8, TadA*8.9, TadA*8.10, TadA*8.11, TadA*8.12, TadA*8.13, TadA*8.14, TadA*8.15,~~

TadA*8.16, TadA*8.17, TadA*8.18, TadA*8.19, TadA*8.20, TadA*8.21, TadA*8.22, TadA*8.23, or TadA*8.24-; and/or

~~100. The base editor system of any one of claims 76-99, wherein the deaminase is a monomer or heterodimer.~~

~~37.101.~~ A polynucleotide encoding the base editor system of any one of claims ~~76-~~
~~100~~30-36.

~~38~~102. A cell produced by the method of ~~any one of claims 1-5~~claim 1 or 3.

~~39~~103. A cell produced by introducing into a cell, or a progenitor thereof, the base editor system of any one of claims ~~76-100~~30-36 or the polynucleotide of claim ~~101~~37.

~~40~~104. The cell of claim ~~102 or 103~~38 or 39, wherein the cell is produced *ex vivo* or *in vitro*;

~~105. The cell any one of claims 102-104, wherein the cell is a hematopoietic stem cell, a CD34+ cell, or a common myeloid progenitor, proerythroblast, or erythroblast-; and/or~~

~~106. The cell of any one of claims 102-104, wherein the cell is a CD34⁺ cell.~~

~~107. The cell of any one of claims 102-104, wherein the cell is a mammalian cell or a human cell.~~

~~108. The cell of claim 107, wherein the cell is a human cell.~~

~~109. An isolated cell or population of cells propagated or expanded from the cell of any one of claims 102-108.~~

~~41~~110. A pharmaceutical composition comprising an effective amount of the cell of any one of claims ~~102-104~~38-40.

~~42~~111. The pharmaceutical composition of claim 41 for use in~~A method of treating a subject with a hemoglobinopathy, hematologic cancer, or myeloproliferative disease-; the method~~

~~comprising administering to the subject the pharmaceutical composition of any one of claims 109 or 110.~~

43. Use of the cell of any one of claims 38-40 in the preparation of a pharmaceutical composition for treating a subject with a hemoglobinopathy, hematologic cancer, or myeloproliferative disease.

~~44.112 The cell of any one of claims 38-40 for use in A method of treating a subject with a hemoglobinopathy, hematologic cancer, or myeloproliferative disease, or the use of claim 43, wherein the method comprising administering to the subject a conditioning regimen comprising an antibody, antibody drug conjugate or chimeric antigen receptor expressing T-cell that selectively binds a cell surface protein is to be administered to the subject, and the cell of any one of claims 103-108, thereby treating the hemoglobinopathy, hematologic cancer, or myeloproliferative disease.~~

~~113. The method of claim 111 or 112, wherein the cell surface protein is CD117 antibody.~~

~~45.114. The cell for use or the use of claim 44, method of claim 111 or 112, wherein the antibody, antibody drug conjugate or chimeric antigen receptor expressing T-cell selectively binds domain 1, 2, 3, 4, or 5 of CD117; optionally,~~

~~115. The method of claim 111 or 112, wherein the antibody is a monoclonal antibody, which is to be administered sequentially or concurrently; and/or~~

~~116. The method of claim 111 or 112, wherein the antibody is administered sequentially or concurrently.~~

~~117. The method of claim 111 or 112, wherein the hemoglobinopathy is sickle cell disease or hereditary persistence of fetal hemoglobin (HPFH); and/or wherein the subject is a mammal or a human.~~

~~118. The method of claim 111 or 112, wherein the cell is autologous to the subject.~~

~~119. The method of claim 111 or 112, wherein the cell is allogenic to the subject.~~

~~120. The method of claim 111 or 112, wherein the subject is a mammal.~~

~~121. The method of claim 111 or 112, wherein the mammal is a human.~~

~~46122. A kit comprising the cell of any one of claims 102-10838-40, the base editor system of any one of claims 76-10030-36, the polynucleotide of claim 10137, or the pharmaceutical composition of any one of claims 109 or 110~~claim 41 or 42.

~~123. The kit of claim 122, further comprising written instructions for the use of the kit in the treatment of a hemoglobinopathy, hematologic cancer, or myeloproliferative disease.~~