

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising two or more immune cells, each immune cell comprising
 - a) a different chimeric antigen receptor that targets an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, wherein the immune cells comprise mutations that reduce or eliminate expression of the targeted antigens; and
 - b) one or more mutations that reduce or eliminate the expression of an immunogenic polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1.
2. The composition of claim 1, wherein one of the immune cells comprises a chimeric antigen receptor that targets CD5 and another immune cell comprises a chimeric antigen receptor that targets an antigen selected from the group consisting of CD7, CD3, CD33, and CD123.
- ~~3. The composition of claim 2, wherein the composition comprises at least three immune cells each comprising a chimeric antigen receptor that targets a different antigen, wherein the targeted antigens are CD3, CD5, and CD7.~~
- ~~4. The composition of claim 1, wherein one of the immune cells expresses a chimeric antigen receptor that targets CD7 and another immune cell expresses a chimeric antigen receptor that targets an antigen selected from the group consisting of CD3, CD33, and CD123.~~
- ~~5. The composition of claim 1, wherein one of the immune cells expresses a chimeric antigen receptor that targets CD3 and another immune cell expresses a chimeric antigen receptor that targets an antigen selected from the group consisting of CD33, and CD123; or~~
- ~~6. The composition of claim 1, wherein one of the immune cells expresses a chimeric antigen receptor that targets CD33 and another immune cell expresses a chimeric antigen receptor that targets CD123.~~

~~7. — The composition of any one of claims 1-6, wherein one immune cell expresses two, three, four or more different chimeric antigen receptors.~~

~~8. — The composition of 7, wherein one of the chimeric antigen receptors targets CD5 and another chimeric antigen receptor targets an antigen selected from the group consisting of CD7, CD3, CD33, and CD123.~~

~~9. — The composition of claim 7, wherein one of the chimeric antigen receptors targets CD7 and another chimeric antigen receptor targets an antigen selected from the group consisting of CD3, CD33, and CD123.~~

~~10. — The composition of claim 7, wherein one of the chimeric antigen receptors targets CD3 and another chimeric antigen receptor targets an antigen selected from the group consisting of CD33, and CD123.~~

~~11. — The composition of claim 7, wherein one of the chimeric antigen receptors targets CD33 and another chimeric antigen receptor targets CD123.~~

~~3.12.~~ A composition comprising:

~~_____~~ at least three immune cells, each comprising a different chimeric antigen receptor, wherein one chimeric antigen receptor targets CD3, one targets CD5, and a third targets CD7, wherein the cells further comprise mutations that reduce or eliminate the expression of the targeted antigens; and further comprise one or more mutations that reduce or eliminate the expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1;

~~13. — A composition comprising~~ at least two immune cells, each comprising a different chimeric antigen receptor, wherein one chimeric antigen receptor targets CD3 and another targets CD7, wherein the cells further comprise mutations that reduce or eliminate the expression of the targeted antigens; and further comprise one or more mutations that reduce or eliminate the

expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1;

~~14. — A composition comprising~~ at least two immune cells, each comprising a different chimeric antigen receptor, wherein one chimeric antigen receptor targets CD5 and another targets CD7, wherein the cells further comprise mutations that reduce or eliminate the expression of the targeted antigens; and further comprise one or more mutations that reduce or eliminate the expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1;

~~15. — A composition comprising~~ at least two immune cells, each comprising a different chimeric antigen receptor, wherein one chimeric antigen receptor targets CD3 and another targets CD5, wherein the cells further comprise mutations that reduce or eliminate the expression of the targeted antigens; and further comprise one or more mutations that reduce or eliminate the expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1; or

~~16. — A composition comprising~~ at least two immune cells, each comprising a different chimeric antigen receptor, wherein one chimeric antigen receptor targets CD33 and another targets CD123, wherein the cells further comprise mutations that reduce or eliminate the expression of the targeted antigen; and further comprise one or more mutations that reduce or eliminate the expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1.

~~4.17.~~ The composition of any one of claims 1-~~16~~3, wherein the mutation is a C to T or A to G mutation that silences the gene or ~~that~~ introduces a stop codon into the gene;

~~18. — The composition of any one of claims 1-17,~~ wherein the mutation introduces a premature stop codon or alters a splice donor or acceptor site;

19. ~~The composition of claim 18, wherein the mutation is generated by a base editor comprising a deaminase domain;~~

20. ~~The composition of claim 19, wherein the mutation is generated by a base editor comprising a deaminase domain that ~~deaminase~~ is a cytidine or an adenosine deaminase; and/or~~

21. ~~The composition of claim 20, wherein the base editor is BE4.~~

22. ~~The composition of any one of claims 1-21, wherein the mutation reduces expression of an encoded polypeptide by about 50% or more relative to a corresponding control cell lacking the mutation.~~

23. ~~The composition of any one of claims 1-22, wherein the composition comprises a population of immune cells.~~

24. ~~The composition of claim 23, wherein at least 50% of the population comprises one or more mutations that reduce or eliminate expression of the targeted antigen and/or the immunogenic polypeptide.~~

5.25. The composition of any one of claims 1-~~24~~4, wherein the immune cells are fratricide resistant;

26. ~~The composition of any one of claims 1-25, wherein the immune cells have increased anti-neoplasia activity;~~

27. ~~The composition of any one of claims 1-26, wherein the immune cells comprise no detectable translocations;~~

28. ~~The composition of any one of claims 1-27, wherein the immune cells comprise less than 1% indels;~~

~~29. The composition of any one of claims 1-28, wherein the immune cell is a mammalian cell, a human cell, or a rodent cell; and/or~~

~~30. The composition of claim 29, wherein the mammalian cell is a human or rodent cell.~~

~~31. The composition of any one of claims 1-30, wherein the immune cell is a cytotoxic T cell, a regulatory T cell, a T helper cell, a dendritic cell, a B cell, or a NK cell, or a progenitor thereof, or a hematopoietic stem cell.~~

~~32. The composition of claim 31, wherein the progenitor is a hematopoietic stem cell.~~

~~6.33.~~ A pharmaceutical composition comprising an effective amount of the composition of any one of claims 1-~~32~~-5 and a pharmaceutically acceptable excipient.

~~7.34.~~ A base editor system comprising a fusion protein comprising a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase domain, and at least two guide polynucleotides each targeting a different antigen, wherein the antigens are selected from the group consisting of CD5, CD7, CD3, CD33, and CD123.

~~8.35.~~ The base editor system of claim ~~7~~34, wherein one guide polynucleotide targets CD5 and another targets an antigen selected from the group consisting of CD7, CD3, CD33, and CD123;

~~36. The base editor system of claim 34, wherein the system comprises~~ing three guide polynucleotides each of which targets one of antigens CD3, CD5, and CD7;

~~37. The base editor system of claim 34, wherein one guide polynucleotide targets CD7 and another targets an antigen selected from the group consisting of CD3, CD33, and CD123;~~

~~38. The base editor system of claim 34, wherein one guide polynucleotide targets CD3 and another targets an antigen selected from the group consisting of CD33, and CD123;~~

~~39. The base editor system of claim 34, wherein one guide polynucleotide targets CD33 and another targets CD123;~~

~~40. The base editor system of claim 34, wherein the guide polynucleotides each comprise a nucleic acid sequence selected from Table 26 or.~~

~~41. The base editor system of claim 40, wherein the guide polynucleotide comprises a nucleic acid sequence selected from AGCGACUGCAGAAAGAAGAG (SEQ ID NO: 1) or CAUACCAGCUGAGCCGUCCG (SEQ ID NO: 2).~~

~~9.42. The base editor system of any one of claims 34-41 claim 7 or 8, wherein the fusion protein further comprises one or more uracil glycosylase inhibitors (UGIs) and/or one or more nuclear localization sequences (NLS);~~

~~43. The base editor system of any one of claims 34-42, wherein the napDNAbp comprises a Cas9, Cas12, Cas12a/Cpf1, Cas12b/C2c1, Cas12c/C2c3, Cas12d/CasY, Cas12e/CasX, Cas12g, Cas12h, Cas12i, or Cas12j/CasΦ polypeptide or a portion thereof;~~

~~44. The base editor system of claim 43, wherein the napDNAbp comprises a Cas12 polypeptide or a fragment thereof.~~

~~45. The base editor system of claim 43, wherein the napDNAbp comprises a Cas9 polypeptide or a fragment thereof which.~~

~~46. The base editor system of claim 45, wherein the Cas9 is a dead Cas9 (dCas9) or a Cas9 nickase (nCas9); or~~

~~47. The base editor system of claim 45, wherein the Cas9 which is a modified Staphylococcus aureus Cas9 (SaCas9), Streptococcus thermophilus 1 Cas9 (St1Cas9), or a modified Streptococcus pyogenes Cas9 (SpCas9).~~

~~10.48.~~ The base editor system of claim ~~945~~, wherein the Cas9 comprises an altered protospacer-adjacent motif (PAM) specificity; optionally,

~~49.~~ ~~The base editor system of claim 48,~~ wherein the altered PAM has specificity for the nucleic acid sequence 5'-NGC-3'.

~~11.50.~~ The base editor system of any one of claims ~~34-49~~7-10, wherein the deaminase domain is capable of deaminating cytidine or adenosine;

~~51.~~ ~~The base editor system of claim 50,~~ wherein the deaminase domain is a cytidine or an adenosine deaminase domain;

~~52.~~ ~~The base editor system of claim 51,~~ wherein the deaminase domain is a cytidine deaminase which is an APOBEC deaminase;

~~53.~~ ~~The base editor system of claim 51,~~ wherein the deaminase domain is an adenosine deaminase which is a TadA variant, which is selected from

~~54.~~ ~~The base editor system of claim 51,~~ wherein the ~~TadA variant is a~~ TadA*8 variant; or

~~55.~~ ~~The base editor system of claim 54,~~ wherein the ~~TadA*8 variant is a~~ 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; or

~~56.~~ ~~The base editor system of claim 53,~~ wherein the ~~wherein the~~ TadA variant is a TadA*9 variant.

~~57.~~ ~~A pharmaceutical composition comprising the base editor system of any one of claims 34-56.~~

~~12.58.~~ A polynucleotide encoding the base editor system and guide polynucleotides of any one of claims ~~34-56~~7-11.

~~13.59.~~ A vector comprising the polynucleotide of claim ~~1258~~;optionally,

~~60.~~—~~The vector of claim 59,~~ wherein the vector is a viral vector, or

~~61.~~—~~The vector of claim 60,~~ wherein the vector is a viral vector ~~is a~~selected from a retroviral vector, an adenoviral vector, a lentiviral vector, a herpesvirus vector, or an adeno-associated viral vector (AAV).

~~14.62.~~ A pharmaceutical composition comprising the polynucleotide of claim ~~1258~~, or the vector of ~~any one of claims 59-61~~claim 13.

~~15.63.~~ A method for producing a CAR-expressing immune cell having reduced immunogenicity, the method comprising expressing in a CAR-expressing immune cell a base editor system comprising a fusion protein comprising a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase domain, and two guide polynucleotides each targeting a polynucleotide encoding a different antigen, wherein the antigens are selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, thereby producing a CAR-expressing immune cell having reduced immunogenicity.

~~16.64.~~ The method of claim ~~1563~~, wherein the immune cell expresses or is contacted with a guide polynucleotide that targets a polynucleotide encoding a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1;and/or wherein the immune cell expresses a chimeric antigen receptor (CAR) that targets an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123.

~~17.65.~~ A method for producing a CAR-expressing immune cell having reduced immunogenicity, the method comprising

(a) expressing in a CAR-expressing immune cell a base editor system comprising a fusion protein comprising a nucleic acid programmable DNA binding protein (napDNAbp) and a deaminase domain; and

(b) contacting the CAR-expressing immune cell with at least two guide polynucleotides each targeting a polynucleotide encoding a different antigen, wherein the antigens are selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, thereby producing a CAR-expressing immune cell having reduced immunogenicity;

a) introducing a mutation that reduces or eliminates the expression of at an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123 into one immune cell and a different mutation in one of said antigens into a second immune cell; and

b) introducing a mutation that reduces or eliminates the expression of at least one polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1 into the immune cells, thereby producing a population of CAR-expressing immune cells having reduced immunogenicity; or

a) introducing a mutation in an endogenous CD5 gene sequence or regulatory element that reduces or eliminates expression of CD5; and

b) expressing in the cell a CD5 CAR construct presented in Table 28.

~~18.66.~~ The method of claim ~~17~~65, the method further comprising contacting the CAR-expressing immune cell with a guide polynucleotide that targets a polynucleotide encoding a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1.

~~67.~~ The method of claim 63 or 64, wherein the immune cell expresses a chimeric antigen receptor (CAR) that targets an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123.

~~68.~~ The method of claim 63 or 64, further comprising introducing a mutation that reduces or eliminates the expression of at least one polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1 into the immune cells,

thereby producing a population of CAR-expressing immune cells having reduced immunogenicity.

69. — A method for producing a population of CAR-expressing immune cells having reduced immunogenicity, the method comprising

a) introducing a mutation that reduces or eliminates the expression of at an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123 into one immune cell and a different mutation in one of said antigens into a second immune cell; and

b) introducing a mutation that reduces or eliminates the expression of at least one polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CHIT1, TRBC1, TRBC2, CD52, B2M, and PD1 into the immune cells, thereby producing a population of CAR-expressing immune cells having reduced immunogenicity.

19.70. The method of claim ~~69~~ 17, wherein the chimeric antigen receptor expressed by the immune cell targets an antigen selected from the group consisting of CD3, CD5, CD7, CD33, and CD123.

20.71. The method of ~~any one of claims 65–68~~ claim 17 or 18, wherein an immune cell produced by the method expresses a chimeric antigen receptor that targets a CD3, CD5, and/or CD7 antigen and fails to express or expresses a reduced level of a CD3, CD5, and/or CD7 antigen;

~~72. — The method of any one of claims 65–68,~~ wherein an immune cell produced by the method expresses a chimeric antigen receptor that targets a CD33 and a CD123 antigen and fails to express or expresses a reduced level of a CD33 and a CD123 antigen;

~~73. — The method of claim 71,~~ wherein the CAR is a CD5 chimeric antigen receptor (CAR); or

~~74. — The method of claim 73,~~ wherein the CAR is a CD5 CAR that is encoded by a CD5 CAR construct presented in Table 28.

75. — ~~A method for producing an immune cell having reduced immunogenicity comprising:~~
~~a) introducing a mutation in an endogenous CD5 gene sequence or regulatory element~~
~~that reduces or eliminates expression of CD5; and~~
~~b) expressing in the cell a CD5 CAR construct presented in Table 28.~~

~~21.76.~~ The method of claim ~~2074~~ or 75, wherein the CD5 CAR construct encodes a CD5 CAR polypeptide that comprises or consists of an amino acid sequence selected from the following:

a)

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1  MEFGLSWLFLVAILKGVQCIDAMGNIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW  60
61  VKQAPGKGLRWMGWINTHTGEPTYADDFKGRFAFSLETSASTAYLQINNLKNEDTATYFC  120
121 TRRGYDWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIKMTQSPSSMYASLGERVTITC  180
181 KASQDINSYLSWFHHKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLDYEDM  240
241 GIYYCQQYDESPWTFGGGTKLEMKGSGDPAEPKSPDKTHTCPGQPREPQVYTLPPSRDEL  300
301 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGSGFFLYSKLTVDKSRWQ  360
361 QGNVFSCSVMEALHNHYTQKSLSLSPGKKDPKFWVLVVVGGVLACYSLLVTVAFIIFWV  420
421 RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQ  480
481 LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE  540
541 RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR  573 (SEQ ID NO: 3);
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b)

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1  MEFGLSWLFLVAILKGVQCIDAMGNIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW  60
61  VKQAPGKGLRWMGWINTHTGEPTYADDFKGRFAFSLETSASTAYLQINNLKNEDTATYFC  120
121 TRRGYDWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIKMTQSPSSMYASLGERVTITC  180
181 KASQDINSYLSWFHHKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLDYEDM  240
241 GIYYCQQYDESPWTFGGGTKLEMKGSGDPATTTAPRPPTPAPTIASQPLSLRPEACRPA  300
301 AGGAVHTRGLDFACDFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPR  360
361 RPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK  420
421 RRGDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT  480
481 KDTYDALHMQALPPR  495 (SEQ ID NO: 4);
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c)

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1  MEFGLSWLFLVAILKGVQCIDAMGNIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW  60
61  VKQAPGKGLRWMGWINTHTGEPTYADDFKGRFAFSLETSASTAYLQINNLKNEDTATYFC  120
121 TRRGYDWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIKMTQSPSSMYASLGERVTITC  180
181 KASQDINSYLSWFHHKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLDYEDM  240
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241 GIYYCQQYDESPWTFGGGKLEMKGSGDPAIEVMYPPPYLDNEKSNGTIIHVKGKHLCP 300
 301 PLFPGPSKPFVWLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR 360
 361 KHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP 420
 421 EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA 480
 481 LHMQUALPPR 489 (SEQ ID NO: 5);

d)

1 MEFGLSWFLVAILKGVQCIDAMGNIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW 60
 61 VKQAPGKGLRWMGWINTHTGEPTYADDFKGRFAFSLETSASTAYLQINNKNEDTATYFC 120
 121 TRRGYDWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIKMTQSPSSMYASLGERVTITC 180
 181 KASQDINSYLSWFHHKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLDYEDM 240
 241 GIYYCQQYDESPWTFGGGKLEMKGSGDPAEPKSPDKTHTCPGQPREPQVYTLPPSRDEL 300
 301 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ 360
 361 QGNVFSCSVMHEALHNHYTQKSLSLSPGKKDKPKTTTPAPRPPTPAPTIASQPLSLRPEA 420
 421 CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR 480
 481 PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL 540
 541 DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST 600
 601 ATKDTYDALHMQALPPR 617 (SEQ ID NO: 6); or

e)

1 MEFGLSWFLVAILKGVQCIDAMGNIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNW 60
 61 VKQAPGKGLRWMGWINTHTGEPTYADDFKGRFAFSLETSASTAYLQINNKNEDTATYFC 120
 121 TRRGYDWYFDVWGAGTTVTVSSGGGGSGGGGSGGGGSDIKMTQSPSSMYASLGERVTITC 180
 181 KASQDINSYLSWFHHKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLDYEDM 240
 241 GIYYCQQYDESPWTFGGGKLEMKGSGDPATTTTPAPRPPTPAPTIASQPLSLRPEACRPA 300
 301 AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT 360
 361 TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRR 420
 421 DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD 480
 481 DALHMQALPPRX 494 (SEQ ID NO: 7).

~~22.77.~~ The method of any one of claims ~~15-21~~⁶³⁻⁷⁶, wherein the immune cell produced by the method exhibits fratricide resistance and/or increased anti-neoplasia activity as compared to a corresponding control cell;

~~78. The method of any one of claims 63-76, wherein the method is carried out *in vivo* in vitro or *ex vivo*;~~

~~79. The method of any one of claims 63-76, wherein the immune cell produced by the method comprises no detectable translocations;~~

~~80. The method of any one of claims 63-76, wherein the immune cell produced by the method comprises less than 1% indels; and/or~~

~~81. The method of any one of claims 63-76, wherein the immune cell produced by the method comprises less than 5% of non-target edits or off-target edits.~~

~~82. The method of any one of claims 63-76, wherein the immune cell produced by the method comprises less than 5% of off target edits.~~

~~23.83.~~ The method of any one of claims ~~15-21~~63-76, wherein the mutation is generated by nucleobase modification;

~~84. The method of claim 83, wherein the mutation is in an exon;~~

~~85. The method of claim 83 or 84, wherein the mutation results in a premature stop codon that reduces or eliminates protein expression;~~

~~86. The method of claim 83 or 84, wherein the mutation is in a splice donor site or a splice acceptor site;~~

~~87. The method of any one of claims 63-76, wherein one or more mutations is generated by contacting a target polynucleotide with a base editor system comprising a fusion protein comprising a nucleic acid programmable DNA binding protein (napDNAbp), a deaminase, and one or more guide polynucleotides; or wherein the mutation reduces expression of an encoded~~

polypeptide by at least about 50% or more relative to a corresponding control cell lacking the mutation.

24.88. The method of any one of claims 15-23~~claim 87~~, wherein the deaminase is an adenosine or cytidine deaminase; or

89.—~~The method of claim 88, wherein the~~ deaminase is a cytidine deaminase which is BE4.

90.—~~The method of claim 87, wherein the mutation reduces expression of an encoded polypeptide by at least about 50% or more relative to a corresponding control cell lacking the mutation.~~

25.91. The method of claim 23~~87~~, wherein the guide polynucleotide comprises a sequence selected from those provided at Table 26; or

92.—~~The method of claim 91, wherein the guide polynucleotide comprises a nucleic acid sequence selected from AGCGACUGCAGAAAGAAGAG (SEQ ID NO: 1) or CAUACCAGCUGAGCCGUCCG (SEQ ID NO: 2);~~ or

93.—~~The method of claim 87, wherein each of the one or more guide nucleic acid sequences targets the napDNAbp to a~~ *CD5*, *FAS*, *LAG-3*, *CD52*, *TRAC*, *B2M*, *CIITA*, *TRBC1*, *TRBC2* and/or a *PDC1/PD-1* gene, or regulatory element; or

94.—~~The method of claim 87, wherein the base editor and one or more guide nucleic acid sequences are introduced into the immune cell via electroporation, nucleofection, cationic lipid-mediated methods, viral transduction, or a combination thereof.~~

26.95. The method of any one of claims 15-25~~63-94~~, further comprising expanding the immune cell in culture to generate a population of immune cells; or

~~96. The method of claim 95, wherein expression of the antigen or polypeptide in the population of immune cells is reduced in at least about 50% of the population of immune cells; and/or~~

~~97. The method of claim 95, further comprising depleting TCR α / β + cells from the population of modified immune cells.~~

~~27.98. A CAR-expressing immune cell having reduced immunogenicity produced by the method of any one of claims 15-2663-97.~~

~~28.99. A pharmaceutical composition comprising the immune cell of claim 2798.~~

~~100. The pharmaceutical composition of claim 99 further comprising a pharmaceutically acceptable excipient.~~

~~29.101. A method for killing a neoplastic cell, the method comprising contacting a neoplastic cell expressing an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, with two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets two of said antigens expressed by the cell, wherein the immune cell comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1.~~

~~102. The method of claim 101, wherein the method is carried out *in vitro* or *in vivo*.~~

~~103. The method of claim 101, wherein the neoplastic cell is derived from a neoplasia.~~

~~30.104. A pharmaceutical composition comprising an effective amount of method for treating a neoplasia in a subject, the method comprising administering to the subject two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets an~~

antigen expressed by a neoplastic cell of ~~the~~ a subject, selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, wherein the immune cell comprises one or more mutations that reduce or eliminate expression of the antigen, and each of the immune cells further comprises one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1, for use in treating a neoplasia in a subject.

31. Use of two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets an antigen expressed by a neoplastic cell of the a subject, selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, in the preparation of a medicament for treating a neoplasia in a subject, wherein the immune cell comprises one or more mutations that reduce or eliminate expression of the antigen, and each of the immune cells further comprises one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1.

~~32.105.~~ The method composition for use of claim 30103 or 104 or the use of claim 31,
wherein the neoplasia is a hematological cancer; or a liquid cancer;

~~106.— The method of claim 105, wherein the neoplasia is a liquid cancer.~~

~~107.— The method of claim 105, wherein the neoplasia is a hematological cancer is selected~~
from leukemia, myeloma, and/or lymphoma;

~~108.— The method of claim 107, wherein the neoplasia is a hematological cancer which is a B~~
cell cancer;

~~109.— The method of claim 105, wherein the neoplasia is a hematological cancer is selected~~
from at least one of the following T-cell acute lymphoblastic leukemia (T-ALL), mycosis
fungoides (MF), Sézary syndrome (SS), Peripheral T/NK-cell lymphoma, Anaplastic large cell
lymphoma ALK⁺, Primary cutaneous T-cell lymphoma, T-cell large granular lymphocytic

leukemia, Angioimmunoblastic T/NK-cell lymphoma, Hepatosplenic T-cell lymphoma, Primary cutaneous CD30⁺ lymphoproliferative disorders, Extranodal NK/T-cell lymphoma, Adult T-cell leukemia/lymphoma, T-cell prolymphocytic leukemia, Subcutaneous panniculitis-like T-cell lymphoma, Primary cutaneous gamma-delta T-cell lymphoma, Aggressive NK-cell leukemia, and Enteropathy-associated T-cell lymphoma;

110.—The method of claim 109, wherein the neoplasia is a hematological cancer which is a T-cell acute lymphoblastic leukemia (T-ALL)-cell or

111.—The method of claim 109, wherein the hematological cancer is acute myelogenous leukemia (AML).

~~33.112. A method~~ The composition for use of claims 30 or 32 or the use of claims 31-32, for treating a neoplasia in a selected subject, the method comprising administering to the selected subject two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets an antigen expressed by a neoplastic cell of the subject, wherein the antigen is selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, wherein the immune cell comprise one or more mutations that reduce or eliminate expression of the antigen, and each of the immune cells further comprise one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CHIT-1, TRBC1, TRBC2, CD52, B2M, and PD1, wherein the subject is selected as having a neoplasia expressing an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123.

113.—The method of claim 109, wherein the hematological cancer is a T-cell acute lymphoblastic leukemia (T-ALL)-cell.

114.—The method of claim 109, wherein the hematological cancer is acute myelogenous leukemia (AML).

115.—The method of any one of claims 101-112, wherein the two or more immune cells expressing different chimeric antigen receptors are administered sequentially.

~~116. — The method of any one of claims 101–112, wherein the two or more immune cells expressing different chimeric antigen receptors are administered simultaneously.~~

~~117. — A method for the antigen-dependent killing of a neoplastic cell in a subject, the method comprising administering to a subject having a neoplasia expressing an antigen selected from the group consisting of CD5, CD7, CD3, CD33, and CD123, two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets one of said antigens, wherein the immune cell comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CHTA, TRBC1, TRBC2, CD52, B2M, and PD1.~~

~~34.118. A The method for the antigen-dependent killing of claim 29, wherein the neoplastic cell is -an acute myelogenous leukemia (AML) cell in a subject, the method comprising administering to a subject having AML expressing CD33 and CD123 antigens, two or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets one of said antigens, wherein the immune cell comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CHTA, TRBC1, TRBC2, CD52, B2M, and PD1.~~

~~35.119. A The method for the antigen-dependent killing of claim 29, wherein the neoplastic cell is a T-cell acute lymphoblastic leukemia (T-ALL) cell in a subject, the method comprising administering to a subject having T-ALL expressing CD3, CD5, and CD7 antigens, at least three immune cells, each immune cell expressing a different chimeric antigen receptor that targets one of said antigens, wherein the immune cell comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CHTA, TRBC1, TRBC2, CD52, B2M, and PD1.~~

~~36.120.~~ ~~A method for treating cancer in a selected subject, the method comprising administering to the subject~~ A pharmaceutical composition comprising at least two immune cells, each immune cell expressing a chimeric antigen receptor that targets CD33 or CD123 antigens, wherein the immune cells comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1, for use in treating cancer in a selected subject, wherein the subject is selected by characterizing the cancer as expressing CD33 and CD123 antigens.

37. Use of at least two immune cells, each immune cell expressing a chimeric antigen receptor that targets CD33 or CD123 antigens, in the preparation of a medicament for treating cancer in a selected subject, wherein the immune cells comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1, and wherein the subject is selected by characterizing the cancer as expressing CD33 and CD123 antigens.

~~38.121.~~ ~~— The method of claim 120,~~ The pharmaceutical composition of claim 36 or the use of claim 37, wherein the cancer expressing CD33 and CD123 antigens is AML.

~~39.122.~~ ~~A method for treating cancer in a selected subject, the method comprising administering to the subject~~ A pharmaceutical composition comprising three or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets CD3, CD5, and CD7 antigens, wherein the immune cells comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1 for use in treating cancer in a selected subject, wherein the subject is selected by characterizing the cancer as expressing CD3, CD5, and CD7 antigens.

40. Use of three or more immune cells, each immune cell expressing a different chimeric antigen receptor that targets CD3, CD5, and CD7 antigens, in the preparation of a medicament

for treating cancer in a selected subject, wherein the immune cells comprise one or more mutations that reduce or eliminate expression of the targeted antigen, and one or more mutations that reduce or eliminate expression of a polypeptide selected from the group consisting of TRAC, LAG-3, FAS, CIITA, TRBC1, TRBC2, CD52, B2M, and PD1, and wherein the subject is selected by characterizing the cancer as expressing CD3, CD5, and CD7 antigens.

41. 123. — The method of claim 122, The pharmaceutical composition of claim 39 or the use of claim 40, wherein the cancer expressing CD3, CD5, and CD7 antigens is T-ALL.

42. 124. The method pharmaceutical composition for use of any one of claims 101 to 123 claim 39 or 41, or the use of claim 40 or 41, wherein the immune cells are cytotoxic T cells, regulatory T cells, T helper cells, dendritic cells, B cells, or NK cells;

125. — The method of any one of claims 101 to 123, wherein the subject has been previously treated with lymphodepletion.; which

126. — The method of claim 125, wherein the lymphodepletion optionally involves administration of cyclophosphamide, fludarabine, and/or alemtuzumab (Cy/Flu/Campath); to be administered;

127. — The method of any one of claims 101 to 126, wherein the subject is refractory to chemotherapy or has a high tumor burden.; or

128. — The method of any one of claims 101 to 127, wherein the subject is subsequently to be treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT).

43. 129. The composition or pharmaceutical composition of any one of claims 1-32 1-6, 14, 30, 32, 33-36, 38-39, 41-42; the use of claims 31-33, 37-38, 40-42; or the method of any one of claims 63-97 or 101-111 15-26, 29, 34 or 35, wherein the immune cell is derived from a single human donor;

~~130.—The method of any one of claims 101–121, wherein the immune cell is autologous to the subject;~~₁

~~131.—The method of any one of claims 101–121, wherein the immune cell is allogenic to the subject;~~₁

~~132.—The method of any one of claims 101–121, wherein the subject is a mammalian subject;~~₁

~~133.—The method of any one of claims 101–121, wherein the subject is a human or rodent subject;~~₁ or

~~134.—The method of any one of claims 101–121, wherein the subject is a pediatric human subject.~~

~~44.135.~~ A kit comprising the composition or the pharmaceutical composition of any one of claims 1-6, 14, 30, 32, 33-36, 38-39 or 41-42~~1-32~~, for use in the treatment of cancer.

~~45.136.~~ A kit comprising the base editor system of any one of claims 7-11~~134-56~~ for use in generating a CAR-expressing immune cell having reduced immunogenicity.

~~137.—The kit of claim 135 or 136, further comprising written instructions for the use of the kit.~~