CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises a CD123 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said CD123 binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in Table 9, Table 2, or Table 6.

2. The isolated nucleic acid molecule of claim 1, wherein said CD123 binding domain further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequence listed in Table 9, Table 2, or Table 6,

optionally wherein said LC CDR1, LC CDR2, and LC CDR3 are the LC CDR sequences listed in Tables 11, 13, 4, or 8.

3. The isolated nucleic acid molecules of claim 1 or 2, wherein said HC CDR1, HC CDR2, and HC CDR3 are the HC CDR sequences listed in Tables 10, 12, 3, or 7.

4. The isolated nucleic acid molecule of any of claims 1-3, which encodes a CAR comprising:

(i) the amino acid sequence of any light chain variable region listed in Table 9 or 2;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any of the light chain variable regions provided in Table 9 or 2; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable regions provided in Table 9 or 2.

5. The isolated nucleic acid molecule of any of claims 1-4, which encodes a CAR comprising:

(i) the amino acid sequence of any heavy chain variable region listed in Table 9 or 2;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable regions provided in Table 9 or 2: or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable regions provided in Table 9 or 2.

6. The isolated nucleic acid molecule of any of claims 1-5, which encodes a CAR comprising the amino acid sequence of any light chain variable region listed in Table 9 or 2, and the amino acid sequence of any heavy chain variable region listed Table 9 or 2,

optionally wherein the encoded CD123 binding domain comprises:

(i) the amino acid sequence selected from a group consisting of SEQ ID NO:480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275.

7. The isolated nucleic acid molecule of any of the preceding claims, wherein the CD123 binding domain comprises a nucleotide sequence selected from a group consisting of SEQ ID NO: 479, 481, 482, 484, or a nucleotide sequence with 95-99% identity thereof,

optionally wherein the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154.

8. The isolated nucleic acid molecule of any of the preceding claims, wherein:

(i) the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, an amino acid sequence comprises at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6; or

(ii) the nucleic acid sequence encoding the transmembrane domain comprises the nucleotide sequence of SEQ ID NO:17, or a nucleotide sequence with 95-99% identity thereof.

9. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded CD123 binding domain is connected to the transmembrane domain by a hinge region, optionally wherein:

(i) the encoded hinge region comprises the amino acid sequence of SEQ ID NO:2, or an amino acid sequence comprising at least one, two, or three modifications, but no more than 20, 10, or 5 modifications, or an amino acid sequence with 95-99% identity thereof; or

(ii) the nucleic acid sequence encoding the hinge region comprises the nucleotide sequence of SEQ ID NO: 13, or a nucleotide sequence with 95-99% identity thereof.

10. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83, optionally wherein:

(i) the encoded costimulatory domain comprises the amino acid sequence of SEQ ID NO:7, or an amino acid sequence having at least one, two or three modifications but not more

than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7, or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7; or

(ii) the nucleic acid sequence encoding the costimulatory domain comprises the nucleotide sequence of SEQ ID NO:18, or a nucleotide sequence with 95-99% identity thereof.

11. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta,

optionally wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10,

optionally wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain,

optionally wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the nucleotide sequence of SEQ ID NO:18, or a nucleotide sequence with 95-99% identity thereof, and/or the nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a nucleotide sequence with 95-99% identity thereof, and

optionally further comprising a leader sequence which encodes the amino acid sequence of SEQ ID NO:1.

12. The isolated nucleic acid molecule of any of the preceding claims, which encodes a CAR comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 99, 100, 101, or 98;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NOs: 99, 100, 101, or 98; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 99, 100, 101, or 98.

13. The isolated nucleic acid molecule of any of the preceding claims, comprising the nucleotide sequence of any of SEQ ID NOs: 39, 40, 41, or 38, or a nucleotide sequence with 95-99% identity to any of SEQ ID NOs: 39, 40, 41, or 38.

14. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1-13.

15. An isolated chimeric antigen receptor (CAR) polypeptide, wherein the CAR comprises an antibody or antibody fragment which includes a CD123 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain, and wherein said CD123 binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequences listed in Table 9, 2 or 6,

optionally wherein said CD123 binding domain further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequences listed in Table 9, 2 or 6.

16. The isolated CAR polypeptide of claim 15, wherein said LC CDR1, LC CDR2, and LC CDR3 are the LC CDR sequences listed in Tables 11, 13, 4 or 8.

17. The isolated CAR polypeptide of any of claim 15 or 16, wherein said HC CDR1, HC CDR2, and HC CDR3 are the HC CDR sequences listed in Tables 10, 12, 3, or 7.

18. The isolated CAR polypeptide of any of claims 15-17, comprising:

(i) the amino acid sequence of any light chain variable region listed in Table 9 or 2;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any of the light chain variable region provided in Table 9 or 2; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable region provided in Table 9 or 2.

19. The isolated CAR polypeptide of any of claims 15-18, comprising:

(i) the amino acid sequence of any heavy chain variable region listed in Table 2 or 9;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable region provided in Table 2 or 9: or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable region provided in Table 2 or 9.

20. The isolated CAR polypeptide of any of claims 15-19, comprising the amino acid sequence of any light chain variable region listed in Table 2 or 9, and the amino acid sequence of any heavy chain variable region listed Table 2 or 9.

21. The isolated CAR polypeptide of any of claims 15-20, comprising:

(i) the amino acid sequence selected from a group consisting of SEQ ID NO: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 480, 483, 485, 478, 158, 159, 160, 157, 217, 218, 219, 216, 276, 277, 278, or 275.

22. The isolated CAR polypeptide of any of claims 15-21, wherein the transmembrane domain comprises a transmembrane domain from a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154.

23. The isolated CAR polypeptide of any of claims 15-22, wherein:

(i) the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6,

(ii) an amino acid sequence comprises at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or

(iii) a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6.

24. The isolated CAR polypeptide of any of claims 15-23, wherein the CD123 binding domain is connected to the transmembrane domain by a hinge region,

optionally wherein the hinge region comprises SEQ ID NO:2, or a sequence with 95-99% identity thereof.

25. The isolated CAR polypeptide of any of claims 15-24, wherein the costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

26. The isolated CAR polypeptide of any of claims 15-25, wherein:

(i) the costimulatory domain comprises the amino acid sequence of SEQ ID NO:7, or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7; or

(ii) the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

27. The isolated CAR polypeptide of any of claims 15-26, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10.

28. The isolated CAR polypeptide of any of claims 15-27, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the amino acid sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

29. The isolated CAR polypeptide of any of claims 15-28, further comprising a leader sequence which comprises the amino acid sequence of SEQ ID NO:1.

30. The isolated CAR polypeptide of any of claims 15-29, comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 99, 100, 101, or 98;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NOs: 99, 100, 101, or 98; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 99, 100, 101, or 98.

31. The nucleic acid molecule of any of claims 1-13, which is a DNA molecule, an RNA molecule, or a combination thereof.

32. The nucleic acid molecule of claim 31, which is an mRNA encoding the CAR polypeptide of claims 14-30.

33. A vector comprising the nucleic acid molecule of any of claims 1-13, or a nucleic acid encoding the CAR polypeptide of any of claims 14-30, wherein the vector is a DNA vector or an RNA vector,

optionally selected from the group consisting of a plasmid, a lentivirus vector, adenoviral vector, and a retrovirus vector, and

optionally further comprising an EF-1 promoter comprising the sequence of SEQ ID NO: 11.

34. A cell, e.g., an immune effector cell, comprising the nucleic acid molecule of any of claims 1-13 or 31-32, the CAR polypeptide of any of claims 14-30, or the vector claim 33.

35. A method of making a cell, e.g., an immune effector cell, comprising introducing into, e.g., transducing, an immune effector cell with the nucleic acid molecule of claims 1-13 or 31-32, or the vector of claim 33.

36. A method of generating a population of cells, comprising introducing RNA into a cell, where the RNA comprises the nucleic acid molecule of any of claims 1-13 or 31-32, or a nucleic acid encoding the CAR polypeptide of any of claims 14-30.

37. Use of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-13, or the CAR polypeptide of any of claims 14-30 in the manufacture of a medicament for providing an anti-tumor immunity in a mammal,

optionally wherein the cell is an autologous T cell or an allogeneic T cell.

38. Use of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-13 or 31-32, or the CAR polypeptide of any of claims 14-30 in the manufacture of a medicament for the treatment of a disease associated with expression of CD123,

optionally wherein the disease associated with CD123 expression is:

(i) a cancer or malignancy,

(ii) a precancerous condition, or

(ii) a non-cancer related indication associated with expression of CD123.

39. The use of the cell according to claim 38, wherein the disease is a hematologic cancer or a pre-leukemia.

40. The use of the cell according to claim 38 or 39, wherein the disease is chosen from one or more of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute lymphoblastic B-cell leukemia (B-cell acute lymphoid leukemia, BALL), acute lymphoblastic T-cell leukemia (T-cell acute lymphoid leukemia (TALL), B-cell prolymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia (CML), hairy cell leukemia, Hodgkin lymphoma, a histiocytic disorder, a mast cell disorder, a myelodysplasia, a myelodysplastic syndrome, a myeloproliferative neoplasm, a plasma cell myeloma, a plasmacytoid dendritic cell neoplasm, or a combination thereof.

41. The use of the cell according to any of claims 37-40, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with one or more of:

(i) an agent that increases the efficacy of the cell comprising the CAR nucleic acid or CAR polypeptide;

(ii) an agent that ameliorates one or more side effects associated with administration of the cell comprising the CAR nucleic acid or CAR polypeptide; or

(iii) an agent that treats the disease associated with the expression of CD123.

42. The use of the cell according to any of claims 37-41, wherein:

(i) the cell, e.g., the population of immune effector cells, comprises an mRNA encoding the CAR polypeptide of claims 14-30; or

(ii) the cell, e.g., the population of immune effector cells, comprises a lentiviral vector comprising the nucleic acid molecule of any of claims 1-13, or encoding the CAR polypeptide of claims 14-30.

43. The use of the cell according to claims 37-40, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with a second therapeutic agent or procedure chosen from one or more of chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, a cytokine, surgical procedure, a

radiation procedure, an agonist of a costimulatory molecule, an inhibitor of an immune checkpoint molecule, a vaccine, or a second CAR-based immunotherapy.

44. The use of the cell according to claims 37-43, wherein:

(i) the cell, e.g., the population of immune effector cells, is to be administered in combination with an agonist of a costimulatory molecule chosen from one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand; or(ii) the cell, e.g., the population of immune effector cells, is to be administered in combination with an inhibitor of an immune checkpoint molecule chosen from one or more of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM-1, CEACAM-3, CEACAM-5, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, or TGFR, e.g., TGFRbeta.

45. The use of the cell according to claim 43, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with a PD-1 inhibitor, a TIM-3 inhibitor, a CEACAM-1 inhibitor, or a combination thereof,

optionally wherein:

(i) the PD-1 inhibitor and the TIM-3 inhibitor are to be administered in combination; or

(ii) the TIM-3 inhibitor and the CEACAM-1 inhibitor are to be administered in combination.

46. The use of the cell according to any of claims 43-45, wherein the agonist or the inhibitor is an antibody molecule, e.g., a monospecific antibody molecule or a bispecific antibody molecule.

47. The use of the cell according to any of claims 43-46, wherein the inhibitor is to be administered subsequent to the administration of the cell, e.g., the population of immune effector cells,

optionally wherein the inhibitor is to be administered about 3-7 days after the administration of the cell, e.g., the population of immune effector cells.

48. The use of the cell according to claims 37-40, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with a CD19 inhibitor,

optionally wherein the CD19 inhibitor is a CD19 CAR-expressing cell or an anti-CD19 antibody molecule.

49. The use of the cell according to any of claims 38-48, wherein the disease is a CD19-negative cancer, e.g., a CD19-negative relapsed cancer.

50. Use of a cell, e.g., a population of immune effector cells, comprising the nucleic acid of any of claims 1-13 or 31-32, or the polypeptide of any of claims 14-30 in the manufacture of a medicament for the prevention of a CD19-negative relapse in a mammal.

51. The use of the cell according to claim 50, wherein the use is to further comprise the administration of a CD19 inhibitor, e.g., a CD19 CAR-expressing cell.

52. The use of the cell according to any of claims 38-51, wherein the disease is a leukemia, e.g., acute lymphoblastic leukemia (e.g., relapsing and refractory ALL), or AML.

53. The use of the cell according to any of claims 48-52, wherein the cell, e.g., the population of immune effector cells, is to be administered after administration of the CD19 inhibitor.

54. The use of the cell according to any of claims 48-52, wherein the cell, e.g., the population of immune effector cells, is to be administered concurrently with the CD19 inhibitor.

55. The use of the cell according to any of claims 37-52 or 54, wherein the cell, e.g., the population of immune effector cells, expresses a CD19 CAR and the CD123 CAR.

56. The use of the cell according to claim 54 or 55, wherein the CD19 CAR or CD123 CAR comprises a split intracellular signaling domain such that full activation of the cell, e.g., the population of immune effector cells, occurs when both the CD19 CAR and CD123 CAR bind to a target cell, e.g., a target CD19+CD123+ cell (e.g., a B-ALL blast cell), compared to activation when the CD19 CAR and CD123 CAR bind to a target cell that expresses one of CD19 or CD123 (e.g., a hematopoietic stem cell).

57. The use of the cell according to claim 56, wherein the CD123CAR comprises a costimulatory domain, e.g., a 4-1BB signaling domain, and the CD19 CAR comprises a primary signaling domain, e.g., a CD3 zeta signaling domain.

58. The use of the cell according to any of claims 37-42, wherein the use is to further comprise the administration of a T cell depleting agent after treatment with the cell, e.g., the population of immune effector cells, thereby reducing (e.g., depleting) the cell (e.g., a CD123CAR-expressing cell).

59. Use of a T cell depleting agent, after treatment of the mammal with a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-13 or 31-32, or the CAR polypeptide of any of claims 14-30 in the preparation of a medicament for the reduction (e.g., depletion) of CD123CAR-expressing cells after a CAR therapy.

60. The use according to claim 58 or 59, wherein the T cell depleting agent is to be administered one, two, three, four, or five weeks after administration of the cell, e.g., the population of immune effector cells.

61. The use according to any of claims 58-60, wherein the mammal has a leukemia, e.g., ALL or AML.

62. The use according to any of claims 58-61, wherein the T cell depleting agent is a CD52 inhibitor,

optionally wherein the CD52 inhibitor is an anti-CD52 antibody molecule, e.g., alemtuzumab.

63. The use according to any of claims 58-62, wherein the cell, e.g., the population of immune effector cells, expresses a CD123CAR polypeptide and a target protein recognized by the T cell depleting agent,

optionally wherein the target protein is CD20, and

optionally wherein the T cell depleting agent is an anti-CD20 antibody, e.g., rituximab.

64. The use according to claim 63, wherein the cell, e.g., the population of immune effector cells, comprises a nucleic acid (e.g., vector) comprising the CD123CAR nucleic acid and a nucleic acid encoding the target protein.

65. The use according to any of claims 37-64, wherein the use is to further comprise the transplantation of a cell, e.g., a hematopoietic stem cell, or a bone marrow, into the mammal.

66. The isolated nucleic acid molecule of any of claims 1-13 or 31-32, the polypeptide of any of claims 14-30, the vector claim 33, or the cell of claim 49 for use as a medicament.

67. The isolated nucleic acid molecule of any of claims 1-13 or 31-32, the polypeptide of any of claims 14-30, the vector of claim 33, or the cell of claim 49 for use in the treatment of a disease associated with expression of CD123.

68. The isolated nucleic acid molecule of any of claims 1-13 or 31-32, the polypeptide of any of claims 14-30, the vector of claim 33, or the cell of claim 49 for use in the treatment of a cancer.

69. The use of claim 67, wherein the disease is chosen from AML, ALL, B-ALL, T-ALL, B-cell prolymphocytic leukemia, chronic lymphocytic leukemia, CML, hairy cell

leukemia, Hodgkin lymphoma, mast cell disorder, myelodysplastic syndrome, myeloproliferative neoplasm, plasma cell myeloma, plasmacytoid dendritic cell neoplasm, or a combination thereof.

70. A cell, e.g., a population of immune effector cells, of claim 49, further expressing a chimeric molecule that comprises a first polypeptide that comprises at least a portion of an inhibitory molecule, associated with a second polypeptide that comprises a positive signal from an intracellular signaling domain,

optionally wherein the chimeric molecule comprise first polypeptide that comprises at least a portion of PD1 and a second polypeptide comprising a costimulatory domain and primary signaling domain.

71. The method of claim 41, wherein the agent is an mTOR inhibitor and the subject is to be administered a low, immune enhancing, dose of an mTOR inhibitor, e.g., RAD001 or rapamycin,

optionally wherein the mTOR inhibitor is to be administered for an amount of time sufficient to decrease the proportion of PD-1 positive T cells, increase the proportion of PD-1 negative T cells, or increase the ratio of PD-1 negative T cells/ PD-1 positive T cells, in the peripheral blood of the subject, or in a preparation of T cells isolated from the subject.

72. The cell comprising the CAR nucleic acid molecule of any of claims 1-13 or 31-32, or the polypeptide of any of claims 14-30, for use in conditioning a subject prior to cell transplantation;

optionally wherein the cell transplantation is a stem cell transplantation, e.g., a hematopoietic stem cell transplantation, or a bone marrow transplantation, and

optionally wherein conditioning a subject prior to cell transplantation comprises reducing the number of CD123-expressing cells in a subject, e.g., CD123-expressing normal cells or CD123-expressing cancer cells.