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 variable domain sequence comprising a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) , further wherein said CD123 binding domain comprises a light chain variable domain sequence comprising a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3), wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino sequences of SEQ ID NO: 487, 492, 497, 502, 507 and 512, respectively; or

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino sequences of SEQ ID NO: 517, 522, 527, 532, 537 and 542, respectively.

2. The isolated nucleic acid molecule of claim 1, which encodes a CAR comprising:

(i) the amino acid sequence of the light chain variable region of SEQ ID NO: 276;

(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 the light chain variable region of SEQ ID NO: 276; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of SEQ ID NO: 276.

3. The isolated nucleic acid molecule of claim 1 or 2, which encodes a CAR comprising:

(i) the amino acid sequence of heavy chain variable region of SEQ ID NO: 217;

(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 the heavy chain variable region of SEQ ID NO: 217; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 217.

4. The isolated nucleic acid molecule of any of claims 1-3, wherein the encoded CD123 binding domain comprises:

(i) the amino acid sequence of SEQ ID NO:480;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to SEQ ID NO: 480; or

(iii) an amino acid sequence with 95-99% identity to SEQ ID NO: 480.

5. 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 and 481, 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.

6. 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.

7. 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.

8. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a costimulatory domain that 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.

9. 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 9599% 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.

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

(i) the amino acid sequence of SEQ ID NO: 99;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to SEQ ID NO: 99; or

(iii) an amino acid sequence with 95-99% identity to SEQ ID NO: 99.

11. The isolated nucleic acid molecule of any of the preceding claims, comprising the nucleotide sequence of SEQ ID NO: 40, or a nucleotide sequence with 95-99% identity to SEQ ID NO: 40.

12. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1-11.

13. 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 variable domain sequence comprising a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3), further wherein said CD123 binding domain further comprises a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3), wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino sequences of SEQ ID NO: 487, 492, 497, 502, 507 and 512, respectively; or

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino sequences of SEQ ID NO: 517, 522, 527, 532, 537 and 542, respectively.

14. The isolated CAR polypeptide of claim 13, comprising:

(i) the amino acid sequence of the light chain variable region of SEQ ID NO: 276;

(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 the light chain variable region of SEQ ID NO: 276; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of SEQ ID NO: 276.

15. The isolated CAR polypeptide of claim 13 or 14, comprising:

(i) the amino acid sequence of the heavy chain variable region of SEQ ID NO: 217;

(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 the heavy chain variable region of SEQ ID NO: 217; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 217.

16. The isolated CAR polypeptide of any of claims 13-15, comprising:

(i) the amino acid sequence of SEQ ID NO: 480;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to SEQ ID NO: 480; or

(iii) an amino acid sequence with 95-99% identity to SEQ ID NO: 480.

17. The isolated CAR polypeptide of any of claims 13-16, 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.

18. The isolated CAR polypeptide of any of claims 13-17, 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.

19. The isolated CAR polypeptide of any of claims 13-18, 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 9599% identity thereof.

20. The isolated CAR polypeptide of any of claims 13-19, 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.

21. The isolated CAR polypeptide of any of claims 13-20, 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 9599% 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.

22. The isolated CAR polypeptide of any of claims 13-21, 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.

23. The isolated CAR polypeptide of any of claims 13-22, 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.

24. The isolated CAR polypeptide of any of claims 13-23, further comprising a leader sequence which comprises the amino acid sequence of SEQ ID NO:1.

25. The isolated CAR polypeptide of any of claims 13-24, comprising:

(i) the amino acid sequence of SEQ ID NO: 99;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to SEQ ID NO: 99; or

(iii) an amino acid sequence with 95-99% identity to SEQ ID NO: 99.

26. The nucleic acid molecule of any of claims 1-11, which is a DNA molecule or an RNA molecule.

27. The nucleic acid molecule of claim 26, which is an mRNA encoding the CAR polypeptide of claims 12-25.

28. A vector comprising the nucleic acid molecule of any of claims 1-11, or a nucleic acid encoding the CAR polypeptide of any of claims 12-25, 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.

29. A cell, e.g., an immune effector cell, comprising the nucleic acid molecule of any of claims 1-11 or 26-27, the CAR polypeptide of any of claims 12-25, or the vector claim 28.

30. An in vitro or ex vivo 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 1-11 or 26-27, or the vector of claim 28.

31. An in vitro or ex vivo 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 1-11 or 26-27, or a nucleic acid encoding the CAR polypeptide of any of claims 1225.

32. Use of a cell, e.g., a population of cells, comprising the nucleic acid molecule of any of claims 1-11, or the CAR polypeptide of any of claims 12-25 in the manufacture of a medicament for providing an anti-tumor immunity in a mammal, wherein the cell is a T cell or an NK cell, optionally wherein the cell is an autologous T cell or an allogeneic T cell.

33. Use of a cell, e.g., a population of cells, comprising the nucleic acid molecule of any of claims 1-11 or 26-27, or the CAR polypeptide of any of claims 12-25 in the manufacture of a medicament for the treatment of a cancer, associated with expression of CD123, wherein the cell is a T cell or an NK cell, optionally wherein the disease associated with CD123 expression is malignancy.

34. The use according to claim 33, wherein the disease is a hematologic cancer.

35. The use according to claim 33 or 34, 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.

36. The use according to any of claims 32-35, wherein the medicament is to be administered in combination with one or more of:

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

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

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

37. The use according to any of claims 32-36, wherein:

(i) the T cell or NK cell, e.g., the population of T cells or NK cells, comprises an mRNA encoding the CAR polypeptide of claims 12-25; or

(ii) the T cell or NK cell, e.g., the population of T cells or NK cells, comprises a lentiviral vector comprising the nucleic acid molecule of any of claims 1-11, or encoding the CAR polypeptide of claims 12-25.

38. The use according to claims 32-35, wherein the medicament 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.

39. The use according to claims 32-38, wherein:

(i) the medicament 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 T cell or NK cell, e.g., the population of T cells or NK 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.

40. The use according to claim 38, wherein the medicament 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.

41. The use according to any of claims 38-40, wherein the agonist or the inhibitor is an antibody molecule, e.g., a monospecific antibody molecule or a bispecific antibody molecule.

42. The use according to any of claims 38-41, wherein the inhibitor is to be administered subsequent to the administration of the T cell or NK cell, e.g., the population of T cells or NK cells, optionally wherein the inhibitor is to be administered about 3-7 days after the administration of the T cell or NK cell, e.g., the population of T cells or NK cells.

43. The use according to claims 32-35, wherein the medicament is to be administered in combination with a CD19 inhibitor, optionally wherein the CD19 inhibitor is a CD19 CAR-expressing T cell or NK cell or an anti-CD19 antibody molecule.

44. The use according to any of claims 33-43, wherein the disease is a CD19-negative cancer, e.g., a CD19-negative relapsed cancer.

45. Use of a T cell or an NK cell, e.g., a population of T cells or NK cells, comprising the nucleic acid of any of claims 1-11 or 26-27, or the polypeptide of any of claims 12-25 in the manufacture of a medicament for the prevention of a CD19-negative relapse cancer in a mammal.

46. The use according to claim 45, wherein the use is to further comprise the administration of a CD19 inhibitor, e.g., a CD19 CAR-expressing T cell or NK cell.

47. The use according to any of claims 33-46, wherein the disease is a leukemia, e.g., acute lymphoblastic leukemia (e.g., relapsing and refractory ALL), or AML.

48. The use according to any of claims 33-47, wherein the medicament is to be administered after administration of the CD19 inhibitor.

49. The use according to any of claims 33-47, wherein the medicament is to be administered concurrently with the CD19 inhibitor.

50. The use according to any of claims 32-41 or 49, wherein the medicament expresses a CD19 CAR and the CD123 CAR.

51. The use of the T cell or NK cell according to claim 50, wherein:

(i) the CD19 CAR comprises a costimulatory domain and the CD123 CAR comprises an intracellular signaling domain, or

(ii) the CD19 CAR comprises an intracellular signaling domain and the CD123 CAR comprises a costimulatory 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).

52. The use according to claim 51, 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.

53. The use according to any of claims 32-37, wherein the medicament is to be administered with a T cell depleting agent, e.g., after the T cell or NK cell has been received by a subject (e.g., human), e.g., the population of immune effector cells, thereby reducing (e.g., depleting) the cell (e.g., a CD123CAR-expressing cell).

54. The use according to claim 53, wherein the T cell depleting agent is to be administered one, two, three, four, or five weeks after administration of the T cell or NK cell, e.g., the population of T or NK cells.

55. The use according to claim 53 or 54, wherein the mammal has a leukemia, e.g., ALL or AML.

56. The use according to any of claims 53-55, wherein the T cell depleting agent is a CD52 inhibitor, optionally wherein the CD52 inhibitor is an anti-CD52 antibody molecule, e.g., alemtuzumab.

57. The use according to any of claims 53-56, wherein the medicament 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.

58. The use according to claim 57, wherein the medicament comprises a nucleic acid (e.g., vector) comprising the CD123CAR nucleic acid and a nucleic acid encoding the target protein.

59. The isolated nucleic acid molecule of any of claims 1-11 or 26-27, the polypeptide of any of claims 12-25, the vector of claim 28, or the T cell or an NK cell of claim 29, for use as a medicament or as a medicament to be taken prior to medical treatment.

60. A T cell or NK cell, e.g., a population of T cells or NK cells, of claim 29, further expressing a chimeric molecule that comprises a first polypeptide that comprises an inhibitory molecule, wherein the inhibitory molecule is chosen from PD-1, PD-L1, CTLA4, TIM-3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR beta; and a second polypeptide that comprises an intracellular signaling domain, wherein the intracellular signaling domain comprises a co-stimulatory intracellular signaling domain derived from 4-1BB, CD27 or CD28, or a primary signaling domain derived from CD3 zeta, or both, optionally wherein the chimeric molecule

comprises a first polypeptide that comprises at least a portion of PD-1 and a second polypeptide comprising a costimulatory domain and primary signaling domain.

61. The use of claim 36, 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.