CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), that specifically binds to CLL-1 chosen from CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12, wherein the CAR comprises a human anti-CLL-1 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said anti-CLL-1 binding domain comprises:

(i) 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 5, 7 or 3; and

(ii). 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 6, 8, or 4.

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

(i) the amino acid sequence of a light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Table 2;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; and/or

(iv) the amino acid sequence of a heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Table 2;

(v) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; or

(vi) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2.

3. The isolated nucleic acid molecule of claim 1 or 2, wherein:

(i) the encoded CLL-1 binding domain comprises the amino acid sequence selected from a group consisting of SEQ ID NO:47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89;

(ii) the encoded CLL-1 binding domain comprises an amino acid sequence having at least one, two or three modifications to any of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89; or

(iii) the encoded CLL-1 binding domain comprises an amino acid sequence with 95-99% identity to any of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89; or

(iv) the CLL-1 binding domain is encoded by a nucleotide sequence selected from a group consisting of SEQ ID NO: 60, 57, 61, 62, or 63, or a sequence with 95-99% identity thereof.

4. The isolated nucleic acid molecule of any of claims 1, 2 or 3, 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.

5. The isolated nucleic acid molecule of any of claims 1, 2, 3 or 4, wherein:

(i) the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, an amino acid sequence comprising 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 a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6;

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

(iii) the nucleic acid sequence encoding the transmembrane domain comprises a sequence encoding a transmembrane domain provided in any of SEQ ID NOs: 112, 109, 113, 114 or 115.

6. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-5, wherein the encoded CLL-1 binding domain is connected to the transmembrane domain by a hinge region.

7. The nucleic acid molecule of claim 6, wherein:

(i) the encoded hinge region comprises the amino acid sequence of SEQ ID NO:2, or a sequence with 95-99% identity thereof;

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

(iii) the nucleic acid sequence encoding the hinge region comprises a sequence encoding a hinge region provided in any of SEQ ID NOs: 112, 109, 113, 114 or 115.

8. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-7, wherein the encoded intracellular signaling domain comprises a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain comprises a functional signaling domain obtained from a costimulatory molecule selected from the group consisting of a MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, 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.

9. The isolated nucleic acid molecule of claim 8, wherein 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 a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7.

10. The isolated nucleic acid molecule of claim 8, wherein the nucleic acid sequence encoding the costimulatory domain comprises the nucleotide sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereof, or the nucleic acid sequence encoding the costimulatory domain comprises a sequence encoding a 4-1BB domain provided in any of SEQ ID NOs: 112,_109, 113, 114 or 115, or a sequence with 95-99% identity thereof.

11. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-10, wherein the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

12. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-11, wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the 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 a 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.

13. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-12, wherein the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the 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.

14. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-13, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereof, and/or

(i) the sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof, or

(ii) the sequence encoding a CD3zeta domain provided in any of SEQ ID NOs: 112, 109, 113, 114 or 115, or a sequence with 95-99% identity thereof.

15. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-14, further comprising a leader sequence which encodes the amino acid sequence of SEQ ID NO:1.

16. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-15, which encodes a CAR comprising:

(i) the amino acid sequence of any of SEQ ID NOs:99, 96, 100, 101, or 102;

(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, 96, 100, 101, or 102; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 99, 96, 100, 101, or 102.

17. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-16, comprising the nucleotide sequence of any of SEQ ID NOs: 112, 109, 113, 114, or 115 , or a nucleotide sequence with 95-99% identity to any of SEQ ID NOs: 112, 109, 113, 114, or 115.

18. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1, 2, 3, or 4-17.

19. An isolated chimeric antigen receptor (CAR) polypeptide, that specifically binds to CLL-1, wherein the CAR comprises an antibody or antibody fragment which includes a human anti-CLL-1 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain, and wherein said anti-CLL-1 binding domain comprises:

(i) 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 5, 7 or 3; and

(ii) 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 6, 8 or 4.

20. The isolated CAR polypeptide of claim 19, comprising:

(i) the amino acid sequence of a light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Table 2;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; and/or

(iv) the amino acid sequence of a heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Table 2;

(v) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2;

(vi) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 provided in Table 2; or

(vii) any one of (i)-(iii) and any one of (iv)-(vi).

21. The isolated CAR polypeptide of claim 19 or 20, comprising:

(i) the amino acid sequence selected from a group consisting of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89;

(ii) an amino acid sequence having at least one, two or three modifications to any of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89.

22. The isolated CAR polypeptide of any of claims 19, 20, or 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 19, 20, or 21-22, 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 19, 20, or 21-23, wherein the CLL-1 binding domain is connected to the transmembrane domain by a hinge region.

25. The isolated CAR polypeptide of claim 24, wherein the hinge region comprises SEQ ID NO:2, or a sequence with 95-99% identity thereof.

26. The isolated CAR polypeptide of any of claims 19, 20, or 21-25, wherein the intracellular signaling domain comprises a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain comprises a functional signaling domain obtained from a costimulatory molecule selected from the group consisting of a MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, 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.

27. The isolated CAR polypeptide of any of claims 19, 20, or 21-26, wherein 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.

28. The isolated CAR polypeptide of any of claims 19, 20, or 21-27, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

29. The isolated CAR polypeptide of any of claims 19, 20, or 21-28, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the 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 a 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.

30. The isolated CAR polypeptide of any of claims 19, 20, or 21-29, wherein the intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the 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.

31. The isolated CAR polypeptide of any of claims 19, 20, or 21-30, further comprising a leader sequence which comprises the amino acid sequence of SEQ ID NO:1.

32. The isolated CAR polypeptide of any of claims 19, 20, or 21-31, comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 99, 96, 100, 101, or 102;

(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, 96, 100, 101, or 102; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 99, 96, 100, 101, or 102.

33. A vector comprising a nucleic acid molecule encoding a CAR of any of claims 19, 20, or 21-32, wherein the vector is selected from the group consisting of a DNA vector, an RNA vector, a plasmid, a lentivirus vector, adenoviral vector, or a retrovirus vector.

34. The vector of claim 33, further comprising an EF-1 promoter comprising the sequence of SEQ ID NO: 11.

35. A cell, e.g., an immune effector cell, comprising the nucleic acid of any of claims 1, 2, 3, or 4-17, the CAR polypeptide of any of claims 18-19, 20, or 21-32, or the vector of claim 33 or 34.

36. A method of making a cell, e.g., an immune effector cell, comprising transducing an immune effector cell with a vector of either of claim 33 or 34.

37. A method of generating a population of RNA-engineered cells, comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, where the RNA comprises a nucleic acid encoding a CAR polypeptide of any of the preceding claims.

38. A cell, e.g., a population of immune effector cells, comprising the CAR nucleic acid of any of claims 1, 2, 3, or 4-17, or the CAR polypeptide of any of claims 18-19, 20, or 21-32 for use in a method of providing an anti-tumor immunity in a mammal.

39. The cell for use according to claim 38, wherein the cell is an autologous T cell or an allogeneic T cell.

40. A cell, e.g., a population of immune effector cells, comprising the CAR nucleic acid of any of claims 1, 2, 3, or 4-17, or the CAR polypeptide of any of claims 18-19, 20, or 21-32 for use in a method of treating a mammal having a disease associated with expression of CLL-1.

41. The cell for use according to claim 40, wherein the disease associated with CLL-1 expression is:

(i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or

(ii) a non-cancer related indication associated with expression of CLL-1.

42. The cell for use according to claim 40 or 41, wherein the disease is a hematologic cancer.

43. The cell for use according to any of claims 40-42, wherein the disease is an acute leukemia chosen from one or more of acute myeloid leukemia (AML); 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), myelodysplastic syndrome, plasma cell myeloma, or a combination thereof.

44. The cell for use according to any of claims 40-43, wherein the cell, e.g., the population of immune effector cells, are 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 CLL-1.

45. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-17, the isolated CAR polypeptide molecule of any of claims 18-19, 20, or 21-32, the vector of either of claim 33 or 34, or the cell of claim 35 for use as a medicament.

46. The isolated nucleic acid molecule of any of claims 1, 2, 3, or 4-17, the isolated CAR polypeptide molecule of any of claims 18-19, 20, or 21-32, the vector of either of claim 33 or 34, or the cell of claim 35 for use in the treatment of a disease associated with expression of CLL-1.

47. A cell, e.g., a population of immune effector cells, of claim 35, further expressing an inhibitory molecule that inhibits T cell function, wherein the molecule comprises:

a first polypeptide that comprises an inhibitory molecule, wherein the inhibitory molecule is chosen from PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR beta, or a fragment thereof; 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.

48. The cell for use according to claim 44, 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.

49. The cell for use according to claim 48, 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.

50. A cell comprising the CAR nucleic acid molecule of any of claims 1, 2, 3, or 4-17 or the CAR polypeptide of any of claims 18-19, 20, or 21-32 for use in a method of conditioning a subject prior to cell transplantation.

51. The cell for use according to claim 50, wherein the cell transplantation is a stem cell transplantation, e.g., a hematopoietic stem cell transplantation, or a bone marrow transplantation.

52. The cell for use according to either of claim 50 or 51, wherein conditioning a subject prior to cell transplantation comprises reducing the number of CLL-1 -expressing cells in a subject, e.g., CLL-1 -expressing normal cells or CLL-1 -expressing cancer cells.

53. A cell, *e.g.*, a population of cells, expressing a chimeric antigen receptor (CAR) that specifically binds to CLL-1, for use in a method of treating a mammal having a disease associated with expression of CLL-1, comprising the administration of an effective amount of cell or population of cells to the mammal, in combination with a chemotherapeutic agent, wherein the chemotherapeutic agent is to be administered prior to administration of the cell, e.g., the population of immune effector cells; and optionally, wherein the chemotherapeutic agent increases CLL-1 expression on the cancer cell or wherein the chemotherapeutic agent is cytarabine.

54. The cell for use of claim 53, wherein the CAR is encoded by a nucleic acid molecule comprising an anti-CLL-1 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said anti-CLL-1 binding domain comprises:

(i) (a) 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 5, 7 or 3; and

(b) 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 an amino acid sequence of CLL-1-CAR9, CLL-1-CAR6, CLL-1-CAR10, CLL-1-CAR11 or CLL-1-CAR12 listed in Tables 6, 8, or 4; or

(ii) (a) the amino acid sequence selected from a group consisting of SEQ ID NO:47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89;

(b) 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: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89;

(c) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 47, 44, 48, 49, 50, 73, 70, 74, 75, 76, 86, 83, 87, 88, or 89; or

(d) a nucleotide sequence selected from a group consisting of SEQ ID NO: 60, 57, 61, 62, or 63, or a sequence with 95-99% identity thereof.

55. The cell for use of claim 53 or 54, wherein:

(i) the chemotherapeutic agent, e.g., cytarabine, is to be administered at least 5 days, 10 days, 15 days, or 30 days prior to administration of the cell, e.g., population of cells, expressing the CAR molecule; or

(ii) the disease associated with expression of CLL-1 is a hematological cancer, e.g., a leukemia, e.g., AML, or a minimal residual disease (MRD) of a hematological cancer.