In another aspect, the invention provides the use of an effective amount of an immunoresponsive cell allogeneic to a subject comprising an inhibitory chimeric antigen receptor that binds an antigen, wherein the binding inhibits the allogeneic immunoresponsive cell in the manufacture of a medicament for modulating a graft versus leukemia response or graft versus tumor response in the subject, wherein the medicament is to be administered to the subject, thereby modulating a graft versus leukemia response or graft versus tumor response in the subject.

In another aspect, the invention provides a T cell comprising:

1) an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cell, and

2) an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cell.

In another aspect, the invention provides the use of an effective amount of T cells comprising an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cells, and an inhibitory chimeric antigen receptor (iCAR) that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cells that comprise the iCAR in the manufacture of a medicament for reducing tumor burden in a subject, wherein the medicament is to be administered to the subject, thereby inducing tumor cell death in the subject.

In another aspect, the invention provides the use of an effective amount of T cells comprising an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cells, and an inhibitory chimeric antigen receptor (iCAR) that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cells that comprise the iCAR in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the medicament is to be administered to the subject, thereby treating or preventing a neoplasia in the subject.

In another aspect, the invention provides the use a method for producing a T cell, the method comprising:

introducing into a T cell a nucleic acid comprising a sequence that encodes an antigen recognizing receptor that binds a first antigen, wherein the binding is capable of activating the cell; and

introducing into the T cell a nucleic acid comprising a sequence that encodes an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding is capable of inhibiting the T cell.

In another aspect, the invention provides an inhibitory chimeric antigen receptor (iCAR) comprising:

(i) an extracellular domain that binds an antigen;

(ii) a transmembrane domain operably linked to the extracellular domain; and

(iii) an intracellular domain that is capable of inducing intracellular signaling to inhibit or prevent the immune activity of a T cell comprising the iCAR, the intracellular domain operably linked to the transmembrane domain.

In another aspect, the invention provides a nucleic acid sequence encoding the inhibitory chimeric antigen receptor as disclosed herein.

In another aspect, the invention provides a vector comprising the nucleic acid sequence as disclosed herein.

In another aspect, the invention provides a composition comprising a nucleic acid having the nucleic acid as disclosed herein or the vector as disclosed herein.

In another aspect, the invention provides a T cell comprising the inhibitory chimeric antigen receptor as disclosed herein, the nucleic acid sequence as disclosed herein, the vector as disclosed herein, or the composition as disclosed herein.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of a T cell as disclosed herein in a pharmaceutically acceptable excipient.

In another aspect, the invention provides a pharmaceutical composition for the treatment of a neoplasia comprising an effective amount of T cells as disclosed herein in a pharmaceutically acceptable excipient.

In another aspect, the invention provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit comprising a T cell comprising an antigen recognizing receptor that binds a first antigen and activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second antigen and inhibits the T cell.

In another aspect, the invention provides the use of an effective amount of T cells allogeneic to the subject comprising an inhibitory chimeric antigen receptor (iCAR) that binds an antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the allogeneic T cells that comprise the iCAR in the manufacture of a medicament for modulating a graft versus leukemia response or graft versus tumor response in a subject, wherein the medicament is to be administered to a subject, thereby modulating a graft versus leukemia response or graft versus tumor response in the subject.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invent ion belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cam bridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

By "activates an immunoresponsive cell" is meant induction of signal transduction or changes in protein expression in the cell resulting in initiation of an immune response. For example, when CD3 Chains cluster in response to ligand binding and immunoreceptor tyrosine-based inhibition motifs (ITAMs) a signal transduction cascade is produced. In certain embodiments, when an endogenous TCR

What is claimed is:

1. An isolated immunoresponsive cell comprising:

1) an antigen recognizing receptor that binds a first antigen, wherein the binding activates the immunoresponsive cell, and

2) an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding inhibits the immunoresponsive cell.

2. The isolated immunoresponsive cell of claim 1, wherein the first antigen is a tumor or pathogen antigen.

3. The isolated immunoresponsive cell of claim 1, wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (FMT) antigen, an organ specific antigen, a blood-brain barrier specific antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), cell surface carbohydrate, mucin type O-glycan.

4. The isolated immunoresponsive cell of any one of claims 1-3, wherein said inhibitory chimeric antigen receptor is recombinantly expressed.

5. The isolated immunoresponsive cell of any one of claims 1-4, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

6. The isolated immunoresponsive cell of any one of claims 1-5, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

7. The isolated immunoresponsive cell of any one of claims 1-6, wherein said antigen recognizing receptor is exogenous or endogenous.

8. The isolated immunoresponsive cell of any one of claims 1-7, wherein said antigen recognizing receptor is recombinantly expressed.

9. The isolated immunoresponsive cell of any one of claims 1-8, wherein the antigen recognizing receptor is expressed from a vector.

10. The isolated immunoresponsive cell of any one of claims 1-9, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a cell of the innate immune system, and a pluripotent stem cell from which lymphoid cells may be differentiated.

11. The isolated immunoresponsive cell of any one of claims 1-10, wherein said immunoresponsive cell is autologous.

12. The isolated immunoresponsive cell of any one of claims 1-10, wherein said immunoresponsive cell is non-autologous.

13. The isolated immunoresponsive cell of any one of claims 1-12, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CDS, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD 123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α , GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

14. The isolated immunoresponsive cell of any one of claims 1-13, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

15. The isolated immunoresponsive cell of claim 14, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain selected from the group consisting of a CD4 polypeptide, a CD8 polypeptide, a CTLA-4 polypeptide, a PD-l polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

16. The isolated immunoresponsive cell of any one of claims l-15, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, scFv, ligand, specific ligand, or polyvalent ligand.

17. The isolated immunoresponsive cell of any one of claims 1-16, wherein the cell expresses a recombinant or an endogenous antigen receptor is selected from the group consisting of 19-28z, P28z, M28z, and 56-28z.

18. Use of an effective amount of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, wherein the binding activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding inhibits the immunoresponsive cell in the manufacture of a medicament for reducing tumor burden in a subject, wherein the medicament is to be administered to the subject, thereby inducing tumor cell death in the subject.

19. The use of claim 18, wherein the medicament selectively targets tumor cells compared to non-tumor cells.

20. The use of claim 18, wherein the medicament reduces the number of tumor cells.

21. The use of claim 18, wherein the medicament reduces tumor size.

22. The use of claim 18, wherein the medicament eradicates the tumor in the subject.

23. Use of an effective amount of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, wherein the binding activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding inhibits the immunoresponsive cell in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the medicament is to be administered to the subject, thereby treating or preventing a neoplasia in the subject.

24. The use of claim 23, wherein the neoplasia is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, non-Hodgkin's lymphoma, ovarian cancer, prostate cancer, pancreatic cancer, lung cancer, breast cancer, and sarcoma, acute myeloid leukemia (AML).

25. The use of any one of claims 17-23, where in the first antigen is a tumor or pathogen antigen.

26. The use of any one of claims 18-25, wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, an organ specific antigen, a blood-brain barrier specific antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region- binding protein 1 (SMAR1), cell surface carbohydrate, or mucin type O-glycan.

27. The use of any one of claims 18-25, wherein said inhibitory chimeric antigen receptor is recombinantly expressed .

28. The use of any one of claims 18-27, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

29. The use of any one of claims 18-28, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

30. The use of any one of claims 18-29, wherein said antigen recognizing receptor is exogenous or endogenous.

31. The use of any one of claims 18-30, wherein said antigen recognizing receptor is recombinantly expressed.

32. The use of any one of claims 18-31, wherein the antigen recognizing receptor is expressed from a vector.

33. The use of any one of claims 18-32, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a cell of the innate immune system, and a pluripotent stem cell from which lymphoid cells may be differentiated.

34. The use of any one of claims 18-33, wherein said immunoresponsive cell is autologous.

35. The use of any one of claims 18-33, wherein said immunoresponsive cell is non-autologous.

36. The use of any one of claims 18-35, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CDS, CD7, CD10,

CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α, GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

37. The use of any one of claims 18-36, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain selected from th group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

38. The use of claim 37, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain selected from the group consisting of a CD4 polypeptide, a CD8 polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

39. The use of any one of claims 18-38, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, scFv, ligand, specific ligand, or polyvalent ligand.

40. The use of any one of claims 18-39, wherein the medicament reduces or eradicates the tumor burden in the subject.

41. The method of any one of claims 18-40, wherein the medicament reduces graft versus host disease (GVHD) in the subject, or a symptom thereof.

42. A method for producing an antigen-specific immunoresponsive cell that comprises an antigen recognizing receptor that binds a first antigen, the method comprising introducing into the immunoresponsive cell a nucleic acid sequence that encodes an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding inhibits the immunoresponsive cell.

43. The method of claim 42, wherein the first antigen is a tumor or pathogen antigen.

44. The method of claim 42 or 43 , wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, an organ specific antigen, a blood-brain barrier specific antigen, E- cadherin, cytokeratin, Opioid - binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region- binding protein 1 (SMAR1), cell surface carbohydrate, or mucin type O-glycan.

45. The method of any one of claims 42-44, wherein said inhibitory chimeric antigen receptor is recombinantly expressed.

46. The method of any one of claims 42-45, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

47. The method of any one of claims 42-46, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

48. The method of any one of claims 42-47, wherein said antigen recognizing receptor is exogenous or endogenous.

49. The method of any one of claim s 42-48, wherein said antigen recognizing receptor is recombinantly expressed.

50. The method of any one of claims 42-49, wherein the antigen recognizing receptor is expressed from a vector.

51. The method of any one of claims 42-50, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a cell of the innate immune system, and a pluripotent stem cell from which lymphoid cells may be differentiated.

52. The method of any one of claims 42-51, wherein said immunoresponsive cell is autologous.

53. The method of any one of claims 42-51, wherein said immunoresponsive cell is autologous.

54. The method of any one of claims 42-53, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CD4, CD7, CD10,

CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α, GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-Al, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

55. The method of any one of claims 42-54, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

56. The method of claim 55, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

57. The method of any one of claims 42-56, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, scFv, ligand, specific ligand, or polyvalent ligand.

58. An inhibitory chimeric antigen receptor (iCAR) comprising:

(i) an extracellular domain that binds an antigen;

(ii) a transmembrane domain operably linked to the extracellular domain; and

(iii) an intracellular domain that activates intracellular signaling to decrease an immune response, the intracellular domain operably linked to the transmembrane domain.

59. The inhibitory chimeric antigen receptor (iCAR) of claim 58, wherein said intracellular signaling domain is selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

60. The inhibitory chimeric antigen receptor (iCAR) of claim 59, wherein said transmembrane domain selected from the group consisting of a CD4 polypeptide, a

CD8 polypeptide, CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

61. The inhibitory chimeric antigen receptor (iCAR) of any one of claims 58-60, further comprising a Fab, scFv, ligand, specific ligand, or polyvalent ligand.

62. The inhibitory chimeric antigen receptor (iCAR) of any one of claims 58-61, wherein the binding of the antigen to the iCAR activates the intracellular signaling domain that decreases an immune response.

63. A nucleic acid sequence encoding an inhibitory chimeric antigen receptor that binds the antigen, wherein the binding activates an intracellular signaling domain that decreases an immune response.

64. A vector comprising a nucleic acid sequence encoding an inhibitory chimeric antigen receptor that binds an antigen, wherein the binding activates an intracellular signaling domain that decreases an immune response.

65. A pharmaceutical composition comprising an effective amount of an immunoresponsive cell of any one of claims 1-17 in a pharmaceutically acceptable excipient.

66. A pharmaceutical composition for use in the treatment of a neoplasia comprising an effective amount of a tumor antigen-specific T cell of any one of claims 1-17 in a pharmaceutically acceptable excipient.

67. A kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit comprising an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen and activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second antigen and inhibits the immunoresponsive cell.

68. The kit of claim 67, wherein the kit further comprises written instructions for using said cell for the treatment of a subject having a neoplasia, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.

69. Use of an effective amount of an immunoresponsive cell allogeneic to a subject comprising an inhibitory chimeric antigen receptor that binds an antigen, wherein the binding inhibits the allogeneic immunoresponsive cell in the manufacture of a medicament for modulating a graft versus leukemia response or graft versus tumor response in the subject, wherein the medicament is to be administered to the subject, thereby modulating a graft versus leukemia response or graft versus tumor response in the subject.

70. The use of claim 69, wherein the allogeneic cell comprises an endogenous T cell receptor.

71. The use of claim 69 or 70, wherein the antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, an organ specific antigen, a blood-brain barrier specific antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), cell surface carbohydrate, or mucin type O-glycan.

72. The use of claim 71, wherein the subject has metastatic breast cancer, hematological malignancy, or a solid tumor, and the human leukocyte antigen (HLA) is HLA-I.

73. The use of claim 71, wherein the subject has a tumor that has undergone epithelium to mesenchymal transition (EMT), and the antigen is one or more of an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, and cytokeratin.

74. The use of any one of claims 69-73, wherein binding of the inhibitory chimeric antigen receptor and the antigen, decreases cell death in a cell comprising the antigen.

75. The use of any one of claims 69-74, wherein the medicament reduces graft versus host disease (GVHD) in the subject, or a symptom thereof.

Claims

1. A T cell comprising:

1) an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cell, and

2) an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cell.

2. The T cell of claim 1, wherein the first antigen comprises a tumor antigen or pathogen antigen.

3. The T cell of claim 1, wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (FMT) antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), or mucin type O-glycan.

4. The T cell of any one of claims 1-3, wherein said inhibitory chimeric antigen receptor is recombinantly expressed.

5. The T cell of any one of claims 1-4, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

6. The T cell of any one of claims 1-5, wherein said antigen recognizing receptor is a T cell receptor (TCR) or a chimeric antigen receptor (CAR).

7. The T cell of any one of claims 1-6, wherein said antigen recognizing receptor is exogenous or endogenous.

8. The T cell of any one of claims 1-7, wherein said antigen recognizing receptor is recombinantly expressed.

9. The T cell of any one of claims 1-8, wherein the antigen recognizing receptor is expressed from a vector.

10. The T cell of any one of claims 1-9, wherein said T cell is autologous.

11. The T cell of any one of claims 1-9, wherein said T cell is non-autologous.

12. The T cell of any one of claims 1-11, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CD5, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD 123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α , GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

13. The T cell of any one of claims 1-12, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain of a polypeptide selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

14. The T cell of claim 13, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain of a polypeptide selected from the group consisting of a CD4 polypeptide, a CD8 polypeptide, a CTLA-4 polypeptide, a PD-l polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

15. The T cell of any one of claims 1-14, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, a scFv, or a ligand.

16. The T cell of any one of claims 1-15, wherein the antigen recognizing receptor comprises a chimeric antigen receptor.

17. The T cell of claim 16, wherein the chimeric antigen receptor is selected from the group consisting of 19-28z, P28z, M28z, and 56-28z.

18. Use of an effective amount of T cells comprising an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cells, and an inhibitory chimeric antigen receptor (iCAR) that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cells that comprise the iCAR in the manufacture of a

medicament for reducing tumor burden in a subject, wherein the medicament is to be administered to the subject, thereby inducing tumor cell death in the subject.

19. The use of claim 18, wherein the medicament selectively targets tumor cells compared to non-tumor cells.

20. The use of claim 18, wherein the medicament reduces the number of tumor cells.

21. The use of claim 18, wherein the medicament reduces tumor size.

22. The use of claim 18, wherein the medicament eradicates the tumor in the subject.

23. Use of an effective amount of T cells comprising an antigen recognizing receptor that binds a first antigen, wherein the binding of the antigen recognizing receptor to the first antigen is capable of activating the T cells, and an inhibitory chimeric antigen receptor (iCAR) that binds a second antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the T cells that comprise the iCAR in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the medicament is to be administered to the subject, thereby treating or preventing a neoplasia in the subject.

24. The use of claim 23, wherein the neoplasia is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, non-Hodgkin's lymphoma, ovarian cancer, prostate cancer, pancreatic cancer, lung cancer, breast cancer, and sarcoma, and acute myeloid leukemia (AML).

25. The use of any one of claims 18-24, where in the first antigen is a tumor or pathogen antigen.

26. The use of any one of claims 18-25, wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), or mucin type O-glycan.

27. The use of any one of claims 18-25, wherein said inhibitory chimeric antigen receptor is recombinantly expressed.

28. The use of any one of claims 18-27, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

29. The use of any one of claims 18-28, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

30. The use of any one of claims 18-29, wherein said antigen recognizing receptor is exogenous or endogenous.

31. The use of any one of claims 18-30, wherein said antigen recognizing receptor is recombinantly expressed.

32. The use of any one of claims 18-31, wherein the antigen recognizing receptor is expressed from a vector.

33. The use of any one of claims 18-32, wherein said T cell is autologous.

34. The use of any one of claims 18-32, wherein said T cell is non-autologous.

35. The use of any one of claims 18-34, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CD5, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α, GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

36. The use of any one of claims 18-35, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

37. The use of claim 36, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain selected from the group consisting of a CD4

polypeptide, a CD8 polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

38. The use of any one of claims 18-37, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, a scFv, or a ligand.

39. The use of any one of claims 18-38, wherein the medicament reduces or eradicates the tumor burden in the subject.

40. The use of any one of claims 18-39, wherein the medicament reduces graft versus host disease (GVHD) in the subject, or a symptom thereof.

41. A method for producing a T cell, the method comprising:

introducing into a T cell a nucleic acid comprising a sequence that encodes an antigen recognizing receptor that binds a first antigen, wherein the binding is capable of activating the cell; and

introducing into the T cell a nucleic acid comprising a sequence that encodes an inhibitory chimeric antigen receptor that binds a second antigen, wherein the binding is capable of inhibiting the T cell.

42. The method of claim 41, wherein the first antigen comprises a tumor or pathogen antigen.

43. The method of claim 41 or 42, wherein the second antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, cytokeratin, Opioid -binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), or mucin type O-glycan.

44. The method of any one of claims 41-43, wherein said inhibitory chimeric antigen receptor is recombinantly expressed.

45. The method of any one of claims 41-44, wherein the inhibitory chimeric antigen receptor is expressed from a vector.

46. The method of any one of claims 41-45, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

47. The method of any one of claims 41-46, wherein said antigen recognizing receptor is exogenous or endogenous.

48. The method of any one of claims 41-47, wherein said antigen recognizing receptor is recombinantly expressed.

49. The method of any one of claims 41-48, wherein the antigen recognizing receptor is expressed from a vector.

50. The method of any one of claims 41-49, wherein said T cell is autologous.

51. The method of any one of claims 41-50, wherein said T cell is non-autologous.

52. The method of any one of claims 41-51, wherein said first antigen is a tumor antigen selected from the group consisting of CD19, CAIX, CEA, CD4, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD123, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-α, GD2, GD3, HER-2, hTERT, IL-13R-α2, κ-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-Al, Mesothelin, Muc-1, Muc-16, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, and WT-1.

53. The method of any one of claims 41-52, wherein said inhibitory chimeric antigen receptor (iCAR) comprises an intracellular signaling domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

54. The method of claim 53, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a transmembrane domain selected from the group consisting of a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

55. The method of any one of claims 41-54, wherein said inhibitory chimeric antigen receptor (iCAR) further comprises a Fab, a scFv, or a ligand.

56. An inhibitory chimeric antigen receptor (iCAR) comprising:

(i) an extracellular domain that binds an antigen;

(ii) a transmembrane domain operably linked to the extracellular domain; and

(iii) an intracellular domain that is capable of inducing intracellular signaling to inhibit or prevent the immune activity of a T cell comprising the iCAR, the intracellular domain operably linked to the transmembrane domain.

57. The inhibitory chimeric antigen receptor (iCAR) of claim 56, wherein the immune response comprises cytokine release, target killing, or proliferation and/or wherein the immune response is stimulated by a CD3 chain ligation or ITAM phosphorylation.

58. The inhibitory chimeric antigen receptor (iCAR) of claim 57 or 58, wherein said intracellular signaling domain comprises a domain ~~is~~ selected from the group consisting of an intracellular portion of a CTLA-4 polypeptide, an intracellular portion of a PD-1 polypeptide, an intracellular portion of a LAG-3 polypeptide, an intracellular portion of a 2B4 polypeptide, and an intracellular portion of a BTLA polypeptide.

59. The inhibitory chimeric antigen receptor (iCAR) of any one of claims 56-58, wherein said transmembrane domain comprises a transmembrane domain of a polypeptide selected from the group consisting of a CD4 polypeptide, a CD8 polypeptide, CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, and a BTLA polypeptide.

60. The inhibitory chimeric antigen receptor (iCAR) of any one of claims 56-59, further comprising a Fab, a scFv, or a ligand.

61. The inhibitory chimeric antigen receptor (iCAR) of any one of claims 56-60, wherein the binding of the antigen to the iCAR is capable of activating the intracellular signaling domain that decreases, suppresses or inhibits the activation of the immune response.

62. A nucleic acid sequence encoding the inhibitory chimeric antigen receptor of any of claims 56-61.

63. A vector comprising the nucleic acid sequence of claim 62.

64. A composition comprising a nucleic acid having the nucleic acid of claim 62 or the vector of claim 63.

65. A T cell comprising the inhibitory chimeric antigen receptor of any one of claims 56-61, the nucleic acid sequence of claim 62, the vector of claim 63, or the composition of claim 64.

66. A pharmaceutical composition comprising an effective amount of a T cell of any one of claims 1-17 in a pharmaceutically acceptable excipient.

67. A pharmaceutical composition for the treatment of a neoplasia comprising an effective amount of T cells of any one of claims 1-17 in a pharmaceutically acceptable excipient.

68. A kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit comprising a T cell comprising an antigen recognizing receptor that binds a first antigen and activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second antigen and inhibits the T cell.

69. The kit of claim 68, wherein the kit further comprises written instructions for using said cell for the treatment of a subject having a neoplasia, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.

70. Use of an effective amount of T cells allogeneic to the subject comprising an inhibitory chimeric antigen receptor (iCAR) that binds an antigen, wherein the binding of the inhibitory chimeric antigen receptor to the second antigen is capable of inhibiting the allogeneic T cells that comprise the iCAR in the manufacture of a medicament for modulating a graft versus leukemia response or graft versus tumor response in a subject, wherein the medicament is to be administered to a subject, thereby modulating a graft versus leukemia response or graft versus tumor response in the subject.

71. The use of claim 70, wherein the allogeneic cell comprises an endogenous T cell receptor.

72. The use of claim 70 or 71, wherein the antigen is CD33, CD38, a human leukocyte antigen (HLA), an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, cytokeratin, Opioid-binding protein/cell adhesion molecule (OPCML), HYLA2, Deleted in Colorectal Carcinoma (DCC), Scaffold/Matrix attachment region-binding protein 1 (SMAR1), or mucin type O-glycan.

73. The use of claim 72, wherein the subject has metastatic breast cancer, hematological malignancy, or a solid tumor, and the human leukocyte antigen (HLA) is HLA-I.

74. The use of claim 72, wherein the subject has a tumor that has undergone epithelium to mesenchymal transition (EMT), and the antigen is one or more of an Epithelial-mesenchymal transition (EMT) antigen, E-cadherin, and cytokeratin.

75. The use of any one of claims 70-74, wherein binding of the inhibitory chimeric antigen receptor to the antigen decreases cell death in a cell comprising the antigen.

76. The use of any one of claims 70-75, wherein the method reduces graft versus host disease (GVHD) in the subject.