includes a Fab, scFv, ligand, specific ligand, or polyvalent ligand. In certain embodiments, the cell expresses a recombinant or an endogenous antigen receptor that is selected from the group consisting of 19-28z, P28z, M28z, and 56-28z.

In various embodiments of the aspects delineated herein, the antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR). In various embodiments of the aspects delineated herein, antigen recognizing receptor is exogenous or endogenous. In various embodiments of the aspects delineated herein, antigen recognizing receptor is recombinantly expressed. In various embodiments of the aspects delineated herein, the antigen recognizing receptor is expressed from a vector. In various embodiments of any of the aspects delineated herein, an allogeneic cell has an endogenous T cell receptor.

In various embodiments of the aspects delineated herein, the cell is one or more 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. In some embodiments, the immunoresponsive cell is autologous. In other embodiments, the immunoresponsive cell is non-autologous.

In another aspect, the invention provides the 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.

In another aspect, the invention provides the 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.

In another aspect, the invention provides a pharmaceutical composition for use in the treatment of a neoplasia comprising an effective amount of a tumor antigen-specific T cell as disclosed herein in a pharmaceutically acceptable excipient.

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.

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

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. ~~A method of reducing tumor burden in a subject, the method comprising administering~~ 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 ~~method~~ use of claim 18, wherein the ~~method~~ medicament selectively targets tumor cells compared to non-tumor cells.

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

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

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

23. ~~A method of increasing survival of a subject having neoplasia, the method comprising administering~~ Use of an effective amount of an immunoresponsive cell comprising an anti-gen recognizing receptor that binds a first antigen, wherein the binding activates the immunoreponsive cell, and an inhibitory chimeric antigen receptor that binds a second anti-gen, 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 ~~method~~ 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 ~~method~~ use of any one of claims 17-23, where in the first antigen is a tumor or pathogen antigen.

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

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

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

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

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

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

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

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

41. The method of any one of claims 18-40, wherein the ~~method~~ 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.

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. ~~A method of modulating a graft versus leukemia response or graft versus tumor response in a subject, the method comprising administering~~ Use of an effective amount of an immunoresponsive cell allogeneic to ~~the~~ 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 ~~method~~ use of claim 69, wherein the allogeneic cell comprises an endogenous T cell receptor.

71. The ~~method~~ use of claim 69 or 70, wherein the antigen is CD33, CD 38, 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ use of any one of claims 69-74, wherein the ~~method~~ medicament reduces graft versus host disease (GVHD) in the subject, or a symptom thereof.