which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity. Optionally one or both nucleic acids may be comprised in a vector, which may be the same vector (bicistronic) or separate vectors. The nucleic acid encoding the CAR and/or the nucleic acid encoding the scFv may each be operably linked to a promoter which may be the same or different promoters. In particular embodiments, the kit further contains written instructions for using the cell for the treatment of a subject having a cancer or disorder.In an additional aspect, the disclosure provides a kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding CD40L. Optionally one or both nucleic acids may be comprised in a vector, which may be the same vector (bicistronic) or separate vectors. The nucleic acid encoding the CAR and/or the nucleic acid encoding CD40L may each be operably linked to a promoter which may be the same or different promoters. In particular embodiments, the kit further contains written instructions for using the cell for the treatment of a subject having a cancer or disorder.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby inducing tumor cell death in the subject.

In an additional aspect, the disclosure provides the use of of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby treating or preventing a neoplasia in the subject.

In an additional aspect, the disclosure provides the use of a T cell comprising an antigen recognizing receptor that binds CD19, in the manufacture of a medicament for treating blood cancer in a subject in need thereof, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds one or more of CD47, PD-1, CTLA-4, and ligands thereof, thereby treating blood cancer in the subject.

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

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing immune-activating cytokine production in response to a cancer cell or a pathogen in a subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing a CD8+ cytotoxic T cell response to a cancer cell or a pathogen in a subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing dendritic cell maturation in a subject having a cancer or having a disease caused by a pathogen.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby inducing tumor cell death in the subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for lengthening survival of a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby lengthening survival of the subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for treating or preventing neoplasia in a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby treating or preventing a neoplasia in the subject.

In an additional aspect, the disclosure provides the nucleic acid comprising sequence encoding a CAR and encoding CD40L, each optionally operably linked to a promoter element.

In various embodiments of any of the aspects delineated herein, 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, and a pluripotent stem cell from which lymphoid cells may be differentiated. In various embodiments of any of the aspects delineated herein, the immunoresponsive cell is autologous.

In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR). In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is exogenous or endogenous. In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is recombinantly expressed. In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is expressed from a vector. In various embodiments of any of the aspects delineated herein, the intracellular signaling domain of the antigen recognizing receptor is the CDζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-IBB, CD28 signaling domain, a portion thereof,

which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity. Optionally one or both nucleic acids may be comprised in a vector, which may be the same vector (bicistronic) or separate vectors. The nucleic acid encoding the CAR and/or the nucleic acid encoding the scFv may each be operably linked to a promoter which may be the same or different promoters. In particular embodiments, the kit further contains written instructions for using the cell for the treatment of a subject having a cancer or disorder.In an additional aspect, the disclosure provides a kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding CD40L. Optionally one or both nucleic acids may be comprised in a vector, which may be the same vector (bicistronic) or separate vectors. The nucleic acid encoding the CAR and/or the nucleic acid encoding CD40L may each be operably linked to a promoter which may be the same or different promoters. In particular embodiments, the kit further contains written instructions for using the cell for the treatment of a subject having a cancer or disorder.

In an additional aspect, the disclosure provides an immunoresponsive cell comprising:

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

2) a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject, wherein the binding activates the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby inducing tumor cell death in the subject.

In an additional aspect, the disclosure provides the use of of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive

activity or immunostimulatory activity, thereby treating or preventing a neoplasia in the subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen in the manufacture of a medicament for treating or preventing a neoplasia in the subject, wherein the binding is capable of activating the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen, thereby treating or preventing a neoplasia in the subject.

In an additional aspect, the disclosure provides a method for producing an immunoresponsive cell as disclosed herein, the method comprising:

(a) introducing into an antigen-specific cell a nucleic acid comprising a sequence that encodes the single-chain variable fragment (scFv) that binds the polypeptide that has immunosuppressive activity or immunostimulatory activity, or

(b) introducing into a cell one or more nucleic acids, which one or more nucleic acids comprise a nucleic acid sequence encoding the antigen recognizing receptor and a nucleic acid sequence encoding the scFv.

In an additional aspect, the disclosure provides the use of a T cell comprising an antigen recognizing receptor that binds CD19 in the manufacture of a medicament for treating blood cancer in a subject in need thereof, wherein the binding is capable of activating the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof, thereby treating blood cancer in the subject.

In an additional aspect, the disclosure provides the use of a T cell comprising an antigen recognizing receptor that binds CD19, in the manufacture of a medicament for treating blood cancer in a subject in need thereof, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds one or more of CD47, PD-1, CTLA-4, and ligands thereof, thereby treating blood cancer in the subject.

In an additional aspect, the disclosure provides a vector comprising (a) a nucleic acid sequence encoding an antigen recognizing receptor that binds a first antigen, and (b) a nucleic acid sequence encoding a soluble single chain variable fragment (scFv) that binds a polypeptide having immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

In an additional aspect, the disclosure provides a pharmaceutical composition comprising an effective amount of an immunoresponsive cell as disclosed herein in a pharmaceutically acceptable excipient.

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

In an additional aspect, the disclosure provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit comprising an immunoresponsive cell comprising (a) an antigen recognizing receptor that binds a first antigen and the binding is capable of activating the immunoresponsive cell, and (b) a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

In an additional aspect, the disclosure provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the neoplasia, pathogen, autoimmune disorder, or transplant to be treated, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

In an additional aspect, the disclosure provides a kit for treatment of a cancer, the kit comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the cancer, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

In an additional aspect, the disclosure provides a kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

In an additional aspect, the disclosure provides a composition comprising (a) a nucleic acid comprising a sequence encoding an antigen recognizing receptor that binds a first antigen and (b) a nucleic acid comprising a sequence encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide having immunosuppressive activity or

immunostimulatory activity, wherein the polypeptide is different from the first antigen, wherein the nucleic acid of (a) and/or the nucleic acid of (b) is optionally a vector.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing immune-activating cytokine production in response to a cancer cell or a pathogen in a subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing a CD8+ cytotoxic T cell response to a cancer cell or a pathogen in a subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing dendritic cell maturation in a subject having a cancer or having a disease caused by a pathogen.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby inducing tumor cell death in the subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for lengthening survival of a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby lengthening survival of the subject.

In an additional aspect, the disclosure provides the use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for treating or preventing neoplasia in a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby treating or preventing a neoplasia in the subject.

In an additional aspect, the disclosure provides the nucleic acid comprising sequence encoding a CAR and encoding CD40L, each optionally operably linked to a promoter element.

In various embodiments of any of the aspects delineated herein, 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, and a pluripotent stem cell from which lymphoid cells may be differentiated. In various embodiments of any of the aspects delineated herein, the immunoresponsive cell is autologous.

In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR). In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is exogenous or endogenous. In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is recombinantly expressed. In various embodiments of any of the aspects delineated herein, the antigen recognizing receptor is expressed from a vector. In various embodiments of any of the aspects delineated herein, the intracellular signaling domain of the antigen recognizing receptor is the CDζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-IBB, CD28 signaling domain, a portion thereof,

What is claimed is:

1. An isolated immunoresponsive cell comprising:

1) an antigen recognizing receptor that binds an antigen, wherein the binding activates the immunoreponsive cell, and

2) a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

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

3. The isolated immunoresponsive cell of claim 1, wherein the soluble scFv is secreted.

4. The isolated immunoresponsive cell of any one of claims 1-3, wherein said antigen recognizing receptor is aT cell receptor (TCR) or chimeric antigen receptor (CAR).

5. The isolated immunoresponsive cell of any one of claims 1-4, wherein said antigen recognizing receptor is exogenous or endogenous.

6. The isolated immunoresponsive cell of any one of claims 1-5, wherein said antigen recognizing receptor is recombinantly expressed.

7. The isolated immunoresponsive cell of any one of claims 1-6, wherein the antigen recognizing receptor is expressed from a vector.

8. The isolated immunoresponsive cell of any one of claims 1-7, wherein the scFv is expressed from a vector.

9. The isolated immunoresponsive cell of any one of claims 1-8, 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, and a pluripotent stem cell from which lymphoid cells may be differentiated.

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

11. The isolated immunoresponsive cell of any one of claims 1-10, wherein said antigen is a tumor antigen selected from the group consisting of CD19, MUC16, MUCl, CAlX, CEA, CDS, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-a, GD2, GD3, HER-2, hTERT, IL-13R-a2, K-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, NKG2D ligands, NY-ES0-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, orWT-1.

12. The isolated immunoresponsive cell of any one of claims 1-11, wherein said immunosuppressive polypeptide is selected from the group consisting of CD47, PD-1, CTLA-4, and ligands thereof.

13. The isolated immunoresponsive cell of any one of claims 1-11, wherein said immunostimulatory polypeptide is selected from the group consisting of CD28, OX-40, 4-1BB, and ligands thereof.

14. The isolated immunoresponsive cell of any one of claims 1-13, wherein said antigen is CD19 or MUC16.

15. The isolated immunoresponsive cell of any one of claims 1-14, wherein the intracellular signaling domain of said antigen recognizing receptor is the CD3ζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-1BB, CD28 signaling domain, or combinations thereof.

16. The isolated immunoresponsive cell of any one of claims 1-15, wherein the cell expresses a recombinant or an endogenous antigen receptor that is 1928z or 4H1128z.

17. The isolated immunoresponsive cell of any one of claims 1-16, wherein the soluble scFv enhances an immune response of the immunoreponsive cell.

18. Use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject, wherein the binding activates

the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby inducing tumor cell death in the subject.

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

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

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

22. Use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for increasing survival of a subject having neoplasia, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby treating or preventing a neoplasia in the subject.

23. The use of claim 22, 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, and ovarian cancer.

24. The use of claim 23, wherein the neoplasia is B cell leukemia, the antigen is CD19, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

25. The use of claim 23, wherein the neoplasia is multiple myeloma, the antigen is CD19, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

26. The use of claim 23, wherein the neoplasia is acute lymphoblastic leukemia (ALL), the antigen is CD19, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

27. The use of claim 23, wherein the neoplasia is chronic lymphocytic leukemia, the antigen is CD19, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

28. The use of claim 23, wherein the neoplasia is non-Hodgkin's lymphoma, the antigen is CD19, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

29. The use of claim 23, wherein the neoplasia is ovarian, the antigen is MUC16, and the polypeptide that has immunosuppressive activity is one or more of CD47, PD-1, CTLA-4, and ligands thereof.

30. The use of any one of claims 22-29, wherein the soluble scFv is secreted.

31. The use of any one of claims 22-30, wherein the scFv is expressed from a vector.

32. The use of any one of claims 22-31, wherein the soluble scFv enhances an immune response of the immunoreponsive cell.

33. The use of any one of claims 22-32, wherein said antigen recognizing receptor is aT cell receptor (TCR) or chimeric antigen receptor (CAR).

34. The use of any one of claims 22-33, wherein said antigen recognizing receptor is exogenous or endogenous.

35. The use of any one of claims 22-34, wherein said antigen recognizing receptor is recombinantly expressed.

36. The use of any one of claims 22-35, wherein the antigen recognizing receptor is expressed from a vector.

37. The use of any one of claims 22-36, wherein the cell is selected from the group consisting of aT cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, and a pluripotent stem cell from which lymphoid cells may be differentiated..

38. The use of any one of claims 22-37, wherein the use reduces or eradicates the tumor burden in the subject.

39. A method for producing an antigen-specific immunoresponsive cell, the method comprising introducing into the immunoresponsive cell

a nucleic acid sequence that encodes a single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the immunoresponsive cell comprises an antigen recognizing receptor that binds an antigen.

40. The method of claim 39, wherein the soluble scFv is secreted.

41. The method of claim 39 or 40, wherein the scFv is expressed from a vector.

42. The method of any one of claims 39-41, wherein the soluble scFv enhances an immune response of the immunoreponsive cell.

43. The method of any one of claims 39-42, wherein said immunosuppressive polypeptide is selected from the group consisting of CD47, PD-1, CTLA-4, and ligands thereof.

44. The method of any one of claims 39-42, wherein said immunostimulatory polypeptide is selected from the group consisting of CD28, OX-40, 4-lBB, and ligands thereof.

45. The method of any one of claims 39-44, wherein said antigen recognizing receptor is aT cell receptor (TCR) or chimeric antigen receptor (CAR).

46. The method of any one of claims 39-45, wherein said antigen recognizing receptor is exogenous or endogenous.

47. The method of any one of claims 39-46, wherein said antigen recognizing receptor is recombinantly expressed.

48. The method of any one of claims 39-47, wherein the antigen recognizing receptor is expressed from a vector.

49. The method of any one of claims 39-48, wherein the cell is selected from the group consisting of aT cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, and a pluripotent stem cell from which lymphoid cells may be differentiated.

50. The method of any one of claims 39-49, wherein the intracellular signaling domain of said antigen recognizing receptor is the CD3ζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-lBB, CD28 signaling domain, or combinations thereof.

51. Use of a T cell comprising an antigen recognizing receptor that binds CD19, in the manufacture of a medicament for treating blood cancer in a subject in need thereof, wherein the binding activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds one or more of CD47, PD-1, CTLA-4, and ligands thereof, thereby treating blood cancer in the subject.

52. The use of claim 51, wherein the blood cancer is selected from the group consisting of B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, and non-Hodgkin's lymphoma.

53. A vector comprising a nucleic acid sequence encoding an antigen recognizing receptor that binds an antigen, and a nucleic acid sequence encoding a soluble single- chain variable fragment (scFv) that binds a polypeptide having immunosuppressive activity or immunostimulatory activity.

54. A pharmaceutical composition comprising an effective amount of an immunoresponsive cell of any one of claims 1-18 in a pharmaceutically acceptable excipient.

55. 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 1-18 in a pharmaceutically acceptable excipient.

56. 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 an antigen and activates the immunoreponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

57. The kit of claim 56, 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.

58. An immunoresponsive cell expressing an antigen binding receptor having immune cell activating activity and exogenous CD40L.

59. The immunoresponsive cell of claim 58, where the antigen binding receptor is a chimeric antigen receptor.

60. The immunoresponsive cell of claim 59, where the chimeric antigen receptor recognizes a tumor antigen.

61. The immunoresponsive cell of any of claims 58-60 where the immunoresponsive cell is selected from the group consisting of a T cell, Natural Killer cell, cytotoxic T cell, and regulatory T cell.

62. Use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing immune-activating cytokine production in response to a cancer cell or a pathogen in a subject.

63. The use of claim 62, where the antigen binding receptor is a chimeric antigen receptor.

64. The use of claim 63, where the chimeric antigen receptor recognizes a cancer antigen.

65. The use of any of claims 62-64 where the immunoresponsive cell is selected from the group consisting of a T cell, Natural Killer cell, cytotoxic T cell, and regulatory T cell.

66. The use of any of claims 62-65, where the cytokine is IL-12.

67. Use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing a CD8+ cytotoxic T cell response to a cancer cell or a pathogen in a subject.

68. The use of claim 67, where the antigen binding receptor is a chimeric antigen receptor.

69. The use of claim 68, where the chimeric antigen receptor recognizes a cancer antigen.

70. The use of any of claims 67-69 where the immunoresponsive cell is selected from the group consisting of a T cell, Natural Killer cell, cytotoxic T cell, and regulatory T cell.

71. Use of an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell or pathogen, respectively, and further expressing exogenous CD40L, in the manufacture of a medicament for increasing dendritic cell maturation in a subject having a cancer or having a disease caused by a pathogen.

72. The use of claim 71, where the antigen binding receptor is a chimeric antigen receptor.

73. The use of claim 72, where the chimeric antigen receptor recognizes a cancer antigen.

74. The use of any of claims 71-73 where the immunoresponsive cell is selected from the group consisting of a T cell, Natural Killer cell, cytotoxic T cell, and regulatory T cell.

75. Use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for reducing tumor burden in a subject ,where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby inducing tumor cell death in the subject.

76. Use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for lengthening survival of a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby lengthening survival of the subject.

77. Use of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, in the manufacture of a medicament for treating or preventing neoplasia in a subject, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby treating or preventing a neoplasia in the subject.

78. A nucleic acid comprising sequence encoding a CAR and encoding CD40L, each optionally operably linked to a promoter element.

79. The nucleic acid of claim 78, comprised in a vector.

80. The nucleic acid of claim 79, where the vector is a virus.

81. A kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant comprising a nucleic acid encoding a CAR which recognizes an antigen of the neoplasia, pathogen, autoimmune disorder, or transplant to be treated, and a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

82. A kit for treatment of a cancer, the kit comprising a nucleic acid encoding a CAR which recognizes an antigen of the cancer, and a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

83. A kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity.

84. A kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and a nucleic acid encoding CD40L.

Claims

1. An immunoresponsive cell comprising:
1) an antigen recognizing receptor that binds a first antigen, wherein the binding is capable of activating the immunoresponsive cell, and
2) a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

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

3. The immunoresponsive cell of claim 1, wherein the soluble scFv is secreted by the cell.

4. The immunoresponsive cell of any one of claims 1-3, wherein said antigen recognizing receptor is a T cell receptor (TCR) or a chimeric antigen receptor (CAR).

5. The immunoresponsive cell of any one of claims 1-4, wherein said antigen recognizing receptor is exogenous or endogenous.

6. The immunoresponsive cell of any one of claims 1-5, wherein said antigen recognizing receptor is recombinantly expressed.

7. The immunoresponsive cell of any one of claims 1-6, wherein the antigen recognizing receptor is expressed from a vector.

8. The immunoresponsive cell of any one of claims 1-7, wherein the scFv is expressed from a vector.

9. The immunoresponsive cell of any one of claims 1-8, wherein the cell is of a type 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, and a pluripotent stem cell from which lymphoid cells may be differentiated.

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

11. The immunoresponsive cell of any one of claims 1-10, wherein said antigen is a tumor antigen selected from the group consisting of CD19, MUC16, MUCl, CAlX, CEA, CDS, CD7, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD133, CD138, a cytomegalovirus (CMV) infected cell antigen, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-a, GD2, GD3, HER-2, hTERT, IL-13R-a2, K-light chain, KDR, LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, NKG2D ligands, NY-ESO-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, ~~or~~ and WT-1.

12. The immunoresponsive cell of any one of claims 1-11, wherein said polypeptide is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and ~~ligands~~ combinations thereof.

13. The immunoresponsive cell of any one of claims 1-11, wherein said polypeptide has immunostimulatory activity and is selected from the group consisting of a CD28 polypeptide and ligands thereof, an OX-40 polypeptide and ligands thereof, a 4-1BB polypeptide and ligands thereof, and combinations thereof.

14. The immunoresponsive cell of any one of claims 1-13, wherein said antigen is CD19 or MUC16.

15. The immunoresponsive cell of any one of claims 1-14, wherein the intracellular signaling domain of said antigen recognizing receptor comprises an intracellular signaling domain of a CD3ζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-1BB, CD28, or combinations thereof.

16. The immunoresponsive cell of any one of claims 1-15, wherein the antigen recognizing receptor that is 1928z or 4H1128z.

17. The immunoresponsive cell of any one of claims 1-16, wherein the soluble scFv enhances an immune response of the immunoresponsive cell.

18. The immunoresponsive cell of claim 16, wherein the 1928z comprises (a) an amino acid sequence having at least 90 %, at least 99 % or at least 95 % identity to SEQ ID NO: 7 (b) the amino acid sequence set forth in SEQ ID NO: 7, optionally without the CDS leader sequence at amino acids 1-18, or (c) a nucleic acid sequence encoded by SEQ ID NO: 8, with or without the leader sequence encoded by SEQ ID NO: 8.

19. The immunoresponsive cell of claim 16 wherein the 4H1128z comprises (a) an amino acid sequence having at least 90 %, at least 99 % or at least 95 % identity to SEQ ID NO: 9, (b) the amino acid sequence set forth in SEQ ID NO: 9, optionally without the CDS leader sequence at amino acids 1-18, or (c) a nucleic acid sequence encoded by SEQ ID NO: 10, with or without the leader sequence encoded by SEQ ID NO: 10.

20. The immunoresponsive cell of any one of claims 1-19, wherein the immunoresponsive cell is a T cell.

21. Use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen in the manufacture of a medicament for reducing tumor burden in a subject, wherein the binding activates the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, thereby inducing tumor cell death in the subject.

22. The use of claim 21, wherein the use reduces the number of tumor cells.

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

24. The use of claim 21, wherein the use eradicates the tumor in the subject.

25. Use of an immunoresponsive cell comprising an antigen recognizing receptor that binds a first antigen in the manufacture of a medicament for treating or preventing a neoplasia in the subject, wherein the binding is capable of activating the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen, thereby treating or preventing a neoplasia in the subject.

26. The use of claim 25, 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, and ovarian cancer.

27. The use of claim 26, wherein the neoplasia is B cell leukemia, the antigen is CD19, and the polypeptide has immunosuppressive activity is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

28. The use of claim 26, wherein the neoplasia is multiple myeloma, the antigen is CD19, and the polypeptide has immunosuppressive activity is of CD47, PD-1, CTLA-4, and ligands thereof.

29. The use of claim 26, wherein the neoplasia is acute lymphoblastic leukemia (ALL), the antigen is CD19, and the polypeptide has immunosuppressive activity is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

30. The use of claim 26, wherein the neoplasia is chronic lymphocytic leukemia, the antigen is CD19, and the polypeptide has immunosuppressive activity is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

31. The use of claim 26, wherein the neoplasia is non-Hodgkin's lymphoma, the antigen is CD19, and the polypeptide has immunosuppressive activity is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

32. The use of claim 26, wherein the neoplasia is ovarian, the antigen is MUC16, and the polypeptide that has immunosuppressive activity is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

33. The use of any one of claims 25-32, wherein the soluble scFv is secreted.

34. The use of any one of claims 25-33, wherein the scFv is expressed from a vector.

35. The use of any one of claims 25-34, wherein the soluble scFv enhances an immune response of the immunoresponsive cell.

36. The use of any one of claims 25-35, wherein said antigen recognizing receptor is a T cell receptor (TCR) or chimeric antigen receptor (CAR).

37. The use of any one of claims 25-36, wherein said antigen recognizing receptor is exogenous or endogenous.

38. The use of any one of claims 25-37, wherein said antigen recognizing receptor is recombinantly expressed.

39. The use of any one of claims 25-38, wherein the antigen recognizing receptor is expressed from a vector.

40. The use of any one of claims 25-39, wherein the cell is of a type 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, and a pluripotent stem cell from which lymphoid cells may be differentiated.

41. The use of any one of claims 25-40, wherein the use reduces or eradicates the tumor burden in the subject.

42. A method for producing an immunoresponsive cell of any one of claims 1-20, the method comprising:

(a) introducing into an antigen-specific cell a nucleic acid comprising a sequence that encodes the single-chain variable fragment (scFv) that binds the polypeptide that has immunosuppressive activity or immunostimulatory activity, or

(b) introducing into a cell one or more nucleic acids, which one or more nucleic acids comprise a nucleic acid sequence encoding the antigen recognizing receptor and a nucleic acid sequence encoding the scFv.

43. The method of claim 42, wherein the soluble scFv is secreted.

44. The method of claim 42 or 43, wherein the scFv is expressed from a vector.

45. The method of any one of claims 42-44, wherein the soluble scFv enhances an immune response of the immunoresponsive cell.

46. The method of any one of claims 42-45, wherein said immunosuppressive polypeptide is selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof.

47. The method of any one of claims 42-45, wherein said immunostimulatory polypeptide is selected from the group consisting a CD28 polypeptide and ligands thereof, an OX-40 polypeptide and ligands thereof, a 4-1BB polypeptide and ligands thereof, and combinations thereof.

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

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

50. The method of any one of claims 42-49, wherein said antigen recognizing receptor is recombinantly expressed.

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

52. The method of any one of claims 42-51, wherein the cell is of a type 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, and a pluripotent stem cell from which lymphoid cells may be differentiated.

53. The method of any one of claims 42-52, wherein the intracellular signaling domain of said antigen recognizing receptor comprises an intracellular signaling domain of a CD3ζ-chain, CD97, CD11a-CD18, CD2, ICOS, CD27, CD154, CDS, OX40, 4-lBB, CD28, or combinations thereof.

54. Use of a T cell comprising an antigen recognizing receptor that binds CD19 in the manufacture of a medicament for treating blood cancer in a subject in need thereof, wherein the binding is capable of activating the immunoresponsive cell, and a soluble single-chain variable fragment (scFv) that binds a polypeptide selected from the group consisting of a CD47 polypeptide and ligands thereof, a PD-1 polypeptide and ligands thereof, a CTLA-4 polypeptide and ligands thereof, and combinations thereof, thereby treating blood cancer in the subject.

55. The use of claim 54, wherein the blood cancer is selected from the group consisting of B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, and non-Hodgkin's lymphoma.

56. A vector comprising (a) a nucleic acid sequence encoding an antigen recognizing receptor that binds a first antigen, and (b) a nucleic acid sequence encoding a soluble single chain variable fragment (scFv) that binds a polypeptide having immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

57. A pharmaceutical composition comprising an effective amount of an immunoresponsive cell of any one of claims 1-20 in a pharmaceutically acceptable excipient.

58. 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 1-20 in a pharmaceutically acceptable excipient.

59. A kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit comprising an immunoresponsive cell comprising (a) an antigen recognizing receptor that binds a first antigen and the binding is capable of activating the immunoresponsive cell, and (b) a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen.

60. The kit of claim 59, 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.

61. A kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the neoplasia, pathogen, autoimmune disorder, or transplant to be treated, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

62. A kit for treatment of a cancer, the kit comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the cancer, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

63. A kit for treatment of a cancer or pathogen-mediated disorder, the kit comprising (a) a nucleic acid encoding a CAR which recognizes an antigen of the cancer or pathogen, and (b) a nucleic acid encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide that has immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the antigen.

64. A composition comprising (a) a nucleic acid comprising a sequence encoding an antigen recognizing receptor that binds a first antigen and (b) a nucleic acid comprising a sequence encoding a soluble single-chain variable fragment (scFv) that binds a polypeptide having immunosuppressive activity or immunostimulatory activity, wherein the polypeptide is different from the first antigen, wherein the nucleic acid of (a) and/or the nucleic acid of (b) is optionally a vector.

65. The vector of claim 56 or the composition of claim 64, wherein:

introduction of the vector into a cell is capable of producing the immunoresponsive cell of any one of claims 1-20; or

introduction of the composition into a cell is capable of producing the immunoresponsive cell of any one of claims 1-20.