involving stimulation of an immune response, such as targeted T cell therapies. Accordingly, novel therapeutic strategies for treating neoplasia are urgently required.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure generally provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and a single-chain variable fragment (scFv) that binds an antigen having immunosuppressive activity (e.g., CD47, PD-1, CTLA-4, and ligands thereof), thereby reducing or eliminating the immunosuppressive activity of the antigen.

The ~~invention~~ disclosure further provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and a single-chain variable fragment (scFv) that binds an antigen having immunostimulatory or proinflammatory activity (e.g., CD28, OX-40, 4-1BB, CD40 and ligands thereof), thereby enhancing the immunostimulatory activity of the antigen.

The ~~invention~~ disclosure further provides immunoresponsive cells (e.g., T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), and regulatory T cells), expressing an antigen binding receptor (e.g., CAR or TCR) having immune cell activating activity and CD40L, for example, exogenous CD40L (CD40L that has been introduced directly or indirectly into the cell (for example, via a vector of naked nucleic acid comprising a nucleic acid sequence encoding CD40L), as compared to endogenous CD40L arising in the cell itself), thereby enhancing the immunostimulatory activity of the antigen.

Accordingly, the ~~invention~~ disclosure provides methods of using such immunoresponsive cells for the treatment of neoplasia, infectious disease, and other pathologies.

In one aspect, the ~~invention~~ disclosure provides an isolated immunoresponsive cell having an antigen recognizing receptor that binds an antigen, where 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.

In another aspect, the ~~invention~~ disclosure provides a method of treating or preventing neoplasia in a subject, the method comprising administering, to the subject, an

effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where 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 neoplasia in the subject. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In another aspect, the ~~invention~~ disclosure provides a method of reducing tumor burden in a subject, the method involving administering, to the subject, an effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where 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 still another aspect, the ~~invention~~ disclosure provides a method of lengthening survival of a subject having neoplasia, the method involving administering, to the subject, an effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where 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 lengthening survival of the subject. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of increasing immune-activating cytokine production in response to a cancer cell in a subject, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell and further expressing exogenous CD40L. In particular non-limiting embodiments, the immune-activating cytokine is selected from the group consisting of. In a particular non-limiting embodiment, the immune-activating cytokine is IL-12. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of increasing immune-activating cytokine production in response to a pathogen in a subject, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the pathogen and further expressing exogenous CD40L. In particular non-limiting embodiments, the immune-activating cytokine is selected from the group consisting of. In a particular non-limiting embodiment, the immune-activating cytokine is IL-12. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of increasing a $CD8^+$ cytotoxic T cell response to a cancer cell in a subject, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the cancer cell and further expressing exogenous CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of increasing a $CD8^+$ cytotoxic T cell response to a pathogen in a subject, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the pathogen and further expressing exogenous CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of promoting dendritic cell maturation in a subject having a cancer, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of a cell of the cancer and further expressing exogenous CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In various non-limiting embodiments, the ~~invention~~ disclosure provides a method of promoting dendritic cell maturation in a subject having a disease caused by a pathogen, comprising administering, to the subject, an immunoresponsive cell having an antigen recognizing receptor that binds an antigen of the pathogen and further expressing exogenous CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In still another aspect, the ~~invention~~ disclosure provides a method of treating or preventing neoplasia in a subject, the method comprising administering, to the subject, an effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby treating or preventing a neoplasia in the subject. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In another aspect, the ~~invention~~ disclosure provides a method of reducing tumor burden in a subject, the method involving administering, to the subject, an effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby inducing tumor cell death in the subject. In still another aspect, the ~~invention~~ disclosure provides a method of lengthening survival of a subject having neoplasia, the method involving administering, to the subject, an effective amount of an immunoresponsive cell having an antigen recognizing receptor that binds a first antigen, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby lengthening survival of the subject.

In yet another aspect, the ~~invention~~ disclosure provides a method of treating blood cancer in a subject in need thereof, the method involving administering to the subject a therapeutically effective amount of a T cell having an antigen recognizing receptor that binds CD19, where 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 non-limiting embodiments, the antigen recognizing receptor is a CAR.

In yet another aspect, the ~~invention~~ disclosure provides a method of treating blood cancer in a subject in need thereof, the method involving administering to the subject a therapeutically effective amount of a T cell having an antigen recognizing receptor that binds CD19, where the binding activates the immunoreponsive cell, and expressing exogenous CD40L, thereby treating blood cancer in the subject. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In one aspect, the ~~invention~~ disclosure provides a method for producing an antigen-specific immunoresponsive cell, the method involving 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, where the immunoresponsive cell has an antigen recognizing receptor that binds an antigen. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In one aspect, the ~~invention~~ disclosure provides a method for producing an antigen-specific immunoresponsive cell, the method involving introducing into the immunoresponsive cell a nucleic acid sequence that encodes CD40L, where the

immunoresponsive cell has an antigen recognizing receptor that binds an antigen. In non-limiting embodiments, the nucleic acid sequence that encodes CD40L is operably linked to a promoter element constitutively or inducibly expressed in the immunoresponsive cell, optionally comprised in a vector. In non-limiting embodiments, the antigen recognizing receptor is a CAR. In non-limiting embodiments, the ~~invention~~ disclosure provides for a nucleic acid comprising sequence encoding a CAR and encoding CD40L, each optionally operably linked to a promoter element constitutively or inducibly expressed in the immunoresponsive cell, and said nucleic acid may optionally be comprised in a vector.In one aspect, the ~~invention~~ disclosure provides a vector having 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. In non-limiting embodiments, the antigen recognizing receptor is a CAR.

In one aspect, the ~~invention~~ disclosure provides a vector having a nucleic acid sequence encoding an antigen recognizing receptor that binds an antigen, and a nucleic acid sequence encoding CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR. In one specific non-limiting embodiment, the invention provides for a retroviral vector containing an anti-CD19 CAR (1928z)- and a CD40L- encoding nucleic acid.

In a related aspect, the ~~invention~~ disclosure provides a pharmaceutical composition containing an effective amount of an immunoresponsive cell of any aspect of the ~~invention~~ disclosure delineated herein in a pharmaceutically acceptable excipient. In another related aspect, the ~~invention~~ disclosure provides a pharmaceutical composition for the treatment of a neoplasia containing an effective amount of a tumor antigen-specific T cell of any aspect of the invention delineated herein in a pharmaceutically acceptable excipient.

In an additional aspect, the ~~invention~~ disclosure provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit containing an immunoresponsive cell having 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. In non-limiting embodiments, the antigen recognizing receptor is a CAR. In particular embodiments, the kit further contains

written instructions for using the cell for the treatment of a subject having a neoplasia, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.

In an additional aspect, the ~~invention~~ disclosure provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit containing an immunoresponsive cell having an antigen recognizing receptor that binds an antigen and activates the immunoreponsive cell, and expressing exogenous CD40L. In non-limiting embodiments, the antigen recognizing receptor is a CAR. In particular embodiments, the kit further contains written instructions for using the cell for the treatment of a subject having a neoplasia, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.

In an additional aspect, the ~~invention~~ disclosure provides a kit for treatment of a neoplasia, pathogen infection, an autoimmune disorder, or an allogeneic transplant, the kit 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. 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 neoplasia, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.

In an additional aspect, the ~~invention~~ disclosure provides 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. 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.

In an additional aspect, the ~~invention~~ 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 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 ~~invention~~ 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,

embodiments of any of the aspects delineated herein, the pharmaceutical composition containing an immunoresponsive cell of the ~~invention~~ disclosure contains a cytokine. In various embodiments of any of the aspects delineated herein, an immunoresponsive cell of the ~~invention~~ disclosure is administered with a cytokine. In various embodiments of any of the aspects delineated herein, the cytokine is one or more of IL-2, IL-3, IL-6, IL-11, IL7, IL12, IL15, IL21, granulocyte macrophage colony stimulating factor, alpha, beta or gamma interferon and erythropoietin.

In various embodiments of any of the aspects delineated herein, the method reduces the number of tumor cells, reduces tumor size, eradicates the tumor in the subject, reduces the tumor burden in the subject, and/or eradicates the tumor burden in the subject.

Illustrative neoplasms for which the ~~invention~~ disclosure can be used include, but are not limited to leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemi a, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, nile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

In various non-limiting embodiments of any of the aspects delineated herein, the neoplasia is one or more of blood cancer, B cell leukemia, multiple myeloma,

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. ~~A method of reducing tumor burden in a subject, the method comprising administering an effective amount~~ 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 ~~method~~ use of claim 18, wherein the ~~method~~ use reduces the number of tumor cells.

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

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

22. ~~A method of increasing survival of a subject having neoplasia, the method comprising administering an effective amount~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ use of any one of claims 22-29, wherein the soluble scFv is secreted.

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

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

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

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

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

37. The ~~method~~ 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 ~~method~~ use of any one of claims 22-37, wherein the ~~method~~ 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. ~~A method of treating blood cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount~~ 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 ~~method~~ 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. ~~A method of increasing immune-activating cytokine production in response to a cancer cell or a pathogen in a subject, comprising administering, to the subject,~~ 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 ~~method~~ use of claim 62, where the antigen binding receptor is a chimeric antigen receptor.

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

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

67. ~~A method of increasing a CD8+ cytotoxic T cell response to a cancer cell or a pathogen in a subject, comprising administering, to the subject,~~ 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 ~~method~~ use of claim 67, where the antigen binding receptor is a chimeric antigen receptor.

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

70. The ~~method~~ 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. ~~A method of increasing dendritic cell maturation in a subject having a cancer or having a disease caused by a pathogen, comprising administering, to the subject,~~ 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 ~~method~~ use of claim 71, where the antigen binding receptor is a chimeric antigen receptor.

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

74. The ~~method~~ 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. ~~A method of reducing tumor burden in a subject comprising administering, to the subject, an effective amount~~ 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. ~~A method of lengthening survival of a subject having neoplasia, the method involving administering, to the subject, an effective amount of~~ 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. ~~A method of treating or preventing neoplasia in a subject, the method involving administering, to the subject, an effective amount of~~ 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.