

FUSION POLYPEPTIDE FOR IMMUNOTHERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 62/876,338, filed July 19, 2019, the content of which is incorporated by reference in its entirety.

SEQUENCE LISTING

This application contains a Sequence Listing, which was submitted in ASCII format via EFS-Web, and is hereby incorporated by reference in its entirety. The ASCII copy, created on July 20, 2020, is named “072734_1102_ST25.txt” and is 126,019 bytes in size.

1. INTRODUCTION

The presently disclosed subject matter provides fusion polypeptides that can improve the activity and efficacy for immunotherapy.

2. BACKGROUND OF THE INVENTION

Cell-based immunotherapy is a therapy with curative potential for the treatment of cancer. T cells and other immune cells may be modified to target tumor antigens through the introduction of genetic material coding for natural or modified T cell receptors (TCR) or synthetic receptors for antigen, termed Chimeric Antigen Receptors (CARs), specific to selected antigens. Patient-engineered CAR T cells have demonstrated remarkable efficacy against a range of liquid and solid malignancies. However, treatment failure and relapses occur in a large fraction of patients. Therefore, there remain needs of improved immunotherapy.

3. SUMMARY ~~OF THE INVENTION~~

In one aspect, the present disclosure refers to a fusion polypeptide comprising:

a) an extracellular domain and a transmembrane domain of a co-stimulatory ligand, and

b) an intracellular domain of a first co-stimulatory molecule.

In another aspect, the present disclosure refers to a nucleic acid encoding a fusion polypeptide as described herein.

In another aspect, the present disclosure refers to a vector comprising the nucleic acid as described herein.

In another aspect, the present disclosure refers to a cell comprising a fusion polypeptide as described herein, the nucleic acid as described herein, or the vector as described herein.

5 In another aspect, the present disclosure refers to a composition comprising an effective amount of a cell as described herein.

In another aspect, the present disclosure refers to a composition comprising: a) a fusion polypeptide as described herein; and b) an antigen-recognizing receptor that binds to an antigen.

10 In another aspect, the present disclosure refers to a nucleic acid composition comprising: a) a first polynucleotide encoding a fusion polypeptide as described herein; and b) a second polynucleotide encoding an antigen-recognizing receptor that binds to an antigen.

In another aspect, the present disclosure refers to a cell comprising the composition as described herein or the nucleic acid composition as described herein.

15 In yet another aspect, the present disclosure refers to a method for producing a cell, the method comprising introducing into a cell a nucleic acid as described herein or a vector as described herein.

20 In yet another aspect, the present disclosure refers to a kit comprising a nucleic acid as described herein, a vector as described herein, a cell as described, or a composition as described herein, or the nucleic acid composition as described herein.

25 In yet another aspect, the present disclosure refers to a use of an effective amount of the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein in the manufacture of a medicament for reducing tumor burden in a subject, wherein the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein is to be administered to the subject.

30 In yet another aspect, the present disclosure refers to a use of an effective amount of the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein in the manufacture of a medicament for treating a subject having a relapse of a neoplasm, wherein the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein is to be administered to the subject.

In yet another aspect, the present disclosure refers to a use of an effective amount of the cells as described herein, or the composition as described herein, or the nucleic

acid composition as described herein in the manufacture of a medicament for treating and/or preventing a neoplasm in a subject, wherein the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein is to be administered to the subject.

5 In yet another aspect, the present disclosure refers to a use of an effective amount of the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein in the manufacture of a medicament for treating and/or preventing an autoimmune disease or an infectious disease in a subject, wherein the cells as described herein, or the composition as described herein, or the nucleic acid
10 composition as described herein is to be administered to the subject.

In yet another aspect, the present disclosure refers to the cells as described herein, or the composition as described herein, or the nucleic acid composition as described herein for use in therapy.

15 The presently disclosed subject matter provides fusion polypeptides that can enhance the activity and efficacy of immunotherapy (e.g., T-cell immunotherapy). In certain examplesembodiments, the fusion polypeptide comprises: a) an extracellular domain and a transmembrane domain of a co-stimulatory ligand, and b) an intracellular domain of a first co-stimulatory molecule.

20 In certain examplesembodiments, the co-stimulatory ligand is selected from the group consisting of tumor necrosis factor (TNF) family members, and immunoglobulin (Ig) superfamily members, and combinations thereof. In certain examplesembodiments, the TNF family member is selected from the group consisting of 4-1BBL, OX40L, CD70, GITRL, CD40L, and combinations thereof. In certain examplesembodiments, the Ig superfamily

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member is selected from the group consisting of CD80, CD86, ICOSLG, and combinations thereof. In certain example embodiments, the co-stimulatory ligand is CD80. In certain example embodiments, the extracellular domain of CD80 comprise an amino acid sequence that is at least about 85% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 1. In certain example embodiments, the extracellular domain of CD80 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 1 or a functional fragment thereof. In certain example embodiments, the extracellular domain of CD80 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 1. In certain example embodiments, the transmembrane domain of CD80 comprise an amino acid sequence that is at least about 85% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 2. In certain example embodiments, the transmembrane domain of CD80 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 2 or a fragment thereof. In certain example embodiments, the transmembrane domain of CD80 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 2.

In certain example embodiments, the first co-stimulatory molecule is selected from the group consisting of CD28, 4-1BB, OX40, ICOS, DAP-10, CD27, CD40, NKG2D, CD2, and combinations thereof. In certain example embodiments, the first co-stimulatory molecule is 4-1BB. In certain example embodiments, the intracellular domain of 4-1BB comprises an amino acid sequence that is at least about 85% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 3. In certain example embodiments, the intracellular domain of 4-1BB comprises or consists of the amino acid sequence set forth in SEQ ID NO: 3 or a functional fragment thereof. In certain example embodiments, the intracellular domain of 4-1BB comprises or consists of the amino acid sequence set forth in SEQ ID NO: 3.

In certain example embodiments, the co-stimulatory ligand is CD80 and the first co-stimulatory molecule is selected from the group consisting of CD28, 4-1BB, OX40, ICOS, DAP-10, CD27, CD40, NKG2D, CD2, and combinations thereof.

In certain example embodiments, the co-stimulatory ligand is CD80 and the first co-stimulatory molecule is 4-1BB. In certain example embodiments, the fusion polypeptide comprises an amino acid sequence that is at least about 85% homologous or identical to the amino acid sequence set forth in SEQ ID NO: 4. In certain example embodiments, the fusion polypeptide comprises or consists of the amino acid sequence set forth in SEQ ID NO: 4.

In certain example embodiments, the fusion polypeptide further comprises an intracellular domain of a second co-stimulatory molecule. In certain example embodiments, the second co-stimulatory molecule is selected from the group consisting of CD28, 4-1BB, OX40,

ICOS, DAP-10, CD27, CD40, NKG2D, CD2, and combinations thereof. In certain

example embodiments, the second co-stimulatory molecule is CD28. In certain

example embodiments, the first co-stimulatory molecule is 4-1BB and the second co-stimulatory molecule is CD28. In certain example embodiments, the intracellular

domain of CD28 comprises an amino acid sequence that is at least about 85%

homologous or identical to the amino acid sequence set forth in SEQ ID NO: 5. In

certain example embodiments, the intracellular domain of CD28 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 5 or a functional fragment thereof. In

certain example embodiments, the intracellular domain of CD28 comprises or consists of the amino acid sequence set forth in SEQ ID NO: 5.

In certain example embodiments, the co-stimulatory ligand is CD80, the first co-stimulatory molecule is 4-1BB, and the second co-stimulatory molecule is CD28. In

certain example embodiments, the fusion polypeptide comprises an amino acid sequence that is at least about 85% homologous or identical to the amino acid sequence set forth in

SEQ ID NO: 6. In certain example embodiments, the fusion polypeptide comprises or consists of the amino acid sequence set forth in SEQ ID NO: 6.

In certain example embodiments, the fusion polypeptide is capable of stimulating a cell comprising an antigen-recognizing receptor. In certain example embodiments, the fusion polypeptide is capable of enhancing the activity of a cell comprising an antigen-recognizing receptor. In certain example embodiments, the activity includes cytotoxicity, cell proliferation, cell persistence, and combinations thereof.

In certain example embodiments, the fusion polypeptide further comprises a signaling domain of a cytokine receptor. In certain example embodiments, the cytokine receptor is selected from the group consisting of CD121a, CDw121b, IL-18Ra, IL18Rb, CD122, CD25, CD132, CD124, CD213a13, CD127, IL-9R, IL15Ra, CDw125, CDw131, CD126, CD130, IL11Ra, Cd114, CD212, CD4, CDw217, CD118, and CDw119.

The presently disclosed subject matter further provides nucleic acid molecules encoding a fusion polypeptide disclosed herein and vectors comprising the nucleic acid molecules.

The presently disclosed subject matter also provides cells comprising the fusion polypeptide, the nucleic acid molecule, or the vector disclosed herein.

In certain example embodiments, the cell further comprises an antigen-recognizing receptor. In certain example embodiments, the antigen recognizing receptor is selected from the group consisting of a chimeric antigen receptor (CAR), a T cell receptor (TCR), and a TCR like fusion molecule.

In certain examplesembodiments, the antigen is a tumor antigen or a pathogen antigen. In certain examplesembodiments, the antigen is a tumor antigen. In certain examplesembodiments, the tumor antigen is selected from the group consisting of CD19, carbonic anhydrase IX (CAIX), carcinoembryonic antigen (CEA), CD8, CD7, CD10, CD20, CD22, CD30, CD33, CLL1, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD133, CD138, CD123, CD44V6, an antigen of a cytomegalovirus (CMV) infected cell (e.g., a cell surface antigen), epithelial glycoprotein-2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), receptor tyrosine-protein kinase Erb-B2, Erb-B3, Erb-B4, folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor- α , Ganglioside G2 (GD2), Ganglioside G3 (GD3), human Epidermal Growth Factor Receptor 2 (HER-2), human telomerase reverse transcriptase (hTERT), Interleukin-13 receptor subunit alpha-2 (IL-13R α 2), κ -light chain, kinase insert domain receptor (KDR), Lewis Y (LeY), L1 cell adhesion molecule (L1CAM), melanoma antigen family A, 1 (MAGE-A1), Mucin 16 (MUC16), Mucin 1 (MUC1), Mesothelin (MSLN), ERBB2, MAGEA3, p53, MART1, GP100, Proteinase3 (PR1), Tyrosinase, Survivin, hTERT, EphA2, NKG2D ligands, cancer-testis antigen NY-ES0-1, oncofetal antigen (h5T4), prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), ROR1, tumor-associated glycoprotein 72 (TAG-72), vascular endothelial growth factor R2 (VEGF-R2), Wilms tumor protein (WT-1), BCMA, NKCS1, EGF1R, EGFR-VIII, CD99, CD70, ADGRE2, CCR1, LILRB2, PRAME CCR4, CD5, CD3, TRBC1, TRBC2, TIM-3, Integrin B7, ICAM-1, CD70, Tim3, CLEC12A, and ERBB. In certain examplesembodiments, the tumor antigen is CD19.

In certain examplesembodiments, the antigen-recognizing receptor is exogenous or endogenous. In certain examplesembodiments, the antigen recognizing receptor is recombinantly expressed. In certain examplesembodiments, the antigen-recognizing receptor is expressed from a vector.

In certain examplesembodiments, the cell is a cell of the lymphoid lineage. In certain examplesembodiments, the cell is a cell of the myeloid lineage. In certain examplesembodiments, the cell of the lymphoid lineage is selected from the group consisting of T cells, Natural Killer (NK) cells, B cells, dendritic cells, and, stem cell from which lymphoid cells may be differentiated. In certain examplesembodiments, the cell is a T cell. In certain examplesembodiments, the T cell is derived from an induced pluripotent stem cell. In certain examplesembodiments, the T cell is a CD8⁺ T cell. In certain examplesembodiments, the CD8⁺ T cell is CD4 independent. In certain examplesembodiments, the T cell is selected from the group consisting of a cytotoxic T

lymphocyte (CTL), a regulatory T cell, a $\gamma\delta$ T cell, a tumor-infiltrating lymphocyte (TIL), and a Natural Killer T (NKT) cell. In certain example embodiments, the fusion polypeptide and the antigen-recognizing receptor are integrated at a locus within the genome of the T cell. In certain example embodiments, the locus is selected from the group consisting of a TRAC locus, a TRBC locus, a TRDC locus, and a TRGC locus. In certain example embodiments, the locus is a TRAC locus or a TRBC locus. In certain example embodiments, the locus is a TRAC locus. In certain example embodiments, the antigen-recognizing receptor is a chimeric antigen receptor (CAR). In certain example embodiments, the expressions of the antigen-recognizing receptor and the fusion polypeptides are under the control of an endogenous promoter. In certain example embodiments, the endogenous promoter is selected from the group consisting of an endogenous TRAC promoter, an endogenous TRBC promoter, an endogenous TRDC promoter, and an endogenous TRGC promoter. In certain example embodiments, the endogenous promoter is a TRAC promoter.

In certain example embodiments, the fusion polypeptide and the antigen-recognizing receptor are integrated within a locus encoding an immune inhibitory molecule. In certain example embodiments, the immune inhibitory molecule is selected from the group consisting of CTLA-4, PD-1, LAG3, BTLA, B7-1, B7-H1, B7-H3, B7-H4, TIM3, SHP-1, SHP-2, TIGIT, CD160, and LAIR1.

In certain example embodiments, the cell is autologous. In certain example embodiments, the cell is allogeneic.

The presently disclosed subject matter provides compositions comprising a cell disclosed herein. In certain example embodiments, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable excipient. In certain example embodiments, the pharmaceutical composition is for treating and/or preventing a neoplasm, an autoimmune disease, and/or an infectious disease. In certain example embodiments, the neoplasm is cancer.

In certain example embodiments, the composition further comprises a regulator that is capable of regulating or modulating expression and/or activity of the fusion polypeptide.

In certain example embodiments, the regulator is selected from the group consisting of promoters that are capable of controlling the expression of the fusion polypeptide, molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory ligand, and molecules that are capable of regulating or modulating expression and activity of the co-stimulatory molecule.

In certain exampleembodiments, the molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory ligand are selected from the group consisting of antibodies that bind to the co-stimulatory ligand, and fusion proteins that bind to the co-stimulatory ligand and regulate or modulate the expression and/or activity of the co-stimulatory ligand.

In certain exampleembodiments, the regulator is an anti-CD80 antibody and the fusion polypeptide comprises an extracellular domain and a transmembrane domain of CD80.

In certain exampleembodiments, the regulator is a fusion protein that binds to CD80 and modulates the activity of CD80 and the fusion polypeptide comprises an extracellular domain and a transmembrane domain of CD80. In certain exampleembodiments, the fusion protein comprises a CTLA-4 fragment that binds to CD80. In certain

exampleembodiments, the CTLA-4 fragment that binds to CD80 is Abatacept or belatacept.

In certain exampleembodiments, the molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory molecule are selected from the group consisting of antibodies that bind to the co-stimulatory molecule, and fusion proteins that bind to the co-stimulatory molecule and regulate or modulate the expression and/or activity of the co-stimulatory molecule.

The presently disclosed subject matter further provides compositions comprising: a) a fusion polypeptide disclosed herein; and b) an antigen-recognizing receptor that binds to an antigen. In certain exampleembodiments, the fusion polypeptide is operably linked to a first promoter. In certain exampleembodiments, the antigen-recognizing receptor is operably linked to a second promoter.

In addition, the presently disclosed subject matter further provides nucleic acid compositions comprising: a) a first polynucleotide encoding a fusion polypeptide disclosed herein; and b) a second polynucleotide encoding an antigen-recognizing receptor that binds to an antigen. In certain exampleembodiments, the nucleic acid composition further comprises a first promoter that is operably linked to the fusion polypeptide. In certain exampleembodiments, the nucleic acid composition further comprises a second promoter that is operably linked to the antigen-recognizing receptor.

In certain exampleembodiments, one or both of the first and second promoters are endogenous or exogenous. In certain exampleembodiments, the exogenous promoter is selected from the group consisting of an elongation factor (EF)-1 promoter, a cytomegalovirus immediate-early promoter (CMV) promoter, a simian virus 40 early promoter (SV40) promoter, a phosphoglycerate kinase (PGK) promoter, and a metallothionein promoter.

In certain exampleembodiments, one or both of the first and second promoters are inducible promoters. In certain exampleembodiment, the inducible promoter is selected from a NFAT transcriptional response element (TRE) promoter, a CD69 promoter, a CD25 promoter, and an IL-2 promoter.

5 The presently disclosed subject matter further provides cells comprising the compositions disclosed herein or the nucleic acid compositions disclosed herein. In certain exampleembodiments, the composition or the nucleic acid composition is integrated at a locus within the genome of the T cell. In certain exampleembodiments, the locus is selected from the group consisting of a TRAC locus, a TRBC locus, a TRDC locus, and a TRGC locus. In certain exampleembodiments, the locus is a TRAC locus or a TRBC locus. In certain exampleembodiments, the composition or the nucleic acid composition is integrated within a locus encoding an immune inhibitory molecule. In certain exampleembodiments, the immune inhibitory molecule is selected from the group consisting of CTLA-4, PD-1, LAG3, BTLA, B7-1, B7-H1, B7-H3, B7-H4, TIM3, SHP-1, SHP-2, TIGIT, CD160, and LAIR1.

15 In certain exampleembodiments, the cells, the compositions, or the nucleic acid compositions disclosed herein are for use in reducing tumor burden, treating and/or preventing a neoplasm, treating and/or preventing an autoimmune disease, treating and/or preventing a pathogen infection (e.g., an infectious disease), and/or treating a subject having a relapse of a neoplasm.

20 The presently disclosed subject matter further provides methods for producing a cell. In certain exampleembodiments, the method comprises introducing into a cell a nucleic acid molecule, a nucleic acid composition, or a vector disclosed herein.

25 The presently disclosed subject matter provides kits comprising a nucleic acid molecule, a vector, a cell, a composition, or a nucleic acid composition disclosed herein. In certain exampleembodiments, the kit further comprises written instructions for treating and/or preventing a neoplasm, a pathogen infection (e.g., an infectious disease), and/or an autoimmune disease.

30 The presently disclosed subject matter provides methods of reducing tumor burden, treating a subject having a relapse of a neoplasm (e.g., a cancer), treating and/or preventing a neoplasm (e.g., a cancer), treating and/or preventing a pathogen infection (e.g., an infectious disease), and/or treating and/or preventing an autoimmune disease, in a subject. In certain exampleembodiments, the method comprises administering to the subject an effective amount of the cells, a composition, or a nucleic acid composition disclosed herein. In certain exampleembodiments, the method reduces the number of tumor cells, reduces

tumor size, and/or eradicates the tumor in the subject. In certain examplesembodiments, the neoplasm or tumor is selected from the group consisting of blood cancers and solid tumors. In certain examplesembodiments, the neoplasm or tumor is a solid tumor. In certain examplesembodiments, 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.

In certain examplesembodiments, the autoimmune disease and infectious disease are selected from the group consisting of rheumatoid arthritis (RA), Type I diabetes, systemic lupus erythematosus (SLE), inflammatory bowel disease, ulcerative colitis, psoriasis, psoriatic arthritis, scleroderma, autoimmune thyroid disease, Grave's disease, Crohn's disease, multiple sclerosis, systemic sclerosis, asthma, organ transplant rejection, a disease or condition associated with transplant, Takayasu arteritis, giant-cell arteritis, Kawasaki disease, polyarteritis nodosa, Behcet's syndrome, Wegener's granulomatosis, ANCA-vasculitides, Churg-Strauss syndrome, microscopic polyangiitis, vasculitis of connective tissue diseases, Hennoch-Schonlein purpura, cryoglobulinemic vasculitis, cutaneous leukocytoclastic angiitis, Sarcoidosis, Cogan's syndrome, Wiskott-Aldrich Syndrome, primary angiitis of the CNS, thromboangiitis obliterans, paraneoplastic arteritis, myelodysplastic syndrome, erythema elevatum diutinum, amyloidosis, autoimmune myositis, Guillain-Barre Syndrome, histiocytosis, atopic dermatitis, pulmonary fibrosis, glomerulonephritis, Whipple's disease, Still's disease, Sjogren's syndrome, osteomyelofibrosis, chronic inflammatory demyelinating polyneuropathy, Kimura's disease, systemic sclerosis, chronic periaortitis, chronic prostatitis, idiopathic pulmonary fibrosis, chronic granulomatous disease, idiopathic, bleomycin-induced lung inflammation, cytarabine-induced lung inflammation, autoimmune thrombocytopenia, autoimmune neutropenia, autoimmune hemolytic anemia, autoimmune lymphocytopenia, chronic autoimmune thyroiditis, autoimmune hepatitis, Hashimoto's thyroiditis, atopic thyroiditis, Graves disease, autoimmune polyglandular syndrome, autoimmune Addison syndrome, and myasthenia gravis.

In certain examplesembodiments, the method further comprises administering to the subject a regulator that is capable of regulating or modulating expression and/or activity of the fusion polypeptide. In certain examplesembodiments, the regulator is selected from the group consisting of promoters that are capable of controlling the expression of the fusion polypeptide, molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory ligand, and molecules that are capable of regulating or

modulating expression and/or activity of the co-stimulatory molecule. In certain example embodiments, the molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory ligand are selected from the group consisting of antibodies that bind to the co-stimulatory ligand, and fusion proteins that bind to the co-stimulatory ligand and regulate or modulate the expression, activity of the co-stimulatory ligand. In certain example embodiments, the regulator is an anti-CD80 antibody and the fusion polypeptide comprises an extracellular domain and a transmembrane domain of CD80. In certain example embodiments, the regulator is a fusion protein that binds to CD80 and modulates the activity of CD80 and the fusion polypeptide comprises an extracellular domain and a transmembrane domain of CD80. In certain example embodiments, the fusion protein is a CTLA4 fragment that binds to CD80. In certain example embodiments, the CTLA4 fragment that binds to CD80 is Abatacept or belatacept.

In certain example embodiments, the molecules that are capable of regulating or modulating expression and/or activity of the co-stimulatory molecule are selected from the group consisting of antibodies that bind to the co-stimulatory molecule, and fusion proteins that bind to the co-stimulatory molecule and regulate or modulate the expression and/or activity of the co-stimulatory molecule.

In certain example embodiments, the regulator is capable of depleting the cell. In certain example embodiments, the regulator is capable of lessening or eliminating one or more side effects associated with administration of the cell. In certain example embodiments, the one or more side effects are selected from the group consisting of off-tumor target effects, cytokine release syndrome, neurotoxicity, and combinations thereof.

In certain example embodiments, the method further comprises administering to the subject a checkpoint immune blockade agent. In certain example embodiments, the checkpoint immune blockade agent is selected from the group consisting of anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TIM3 antibodies, and combinations thereof. In certain example embodiments, the checkpoint immune blockade agent is an anti-PD-1 antibody.

4. BRIEF DESCRIPTION OF THE FIGURES

The following Detailed Description, given by way of example, but not intended to limit the presently disclosed subject matter to specific embodiments described, may be understood in conjunction with the accompanying drawings.

Figure 1 depicts a cell in accordance with certain embodiments of the presently disclosed subject matter.