SELF-POLARIZING IMMUNE CELLS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/144,860, filed February 2, 2021, the entirety of which is incorporated herein by reference.

SEQUENCE LISTING

[0000] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 27, 2022, is named 2012851-0124_SL.txt and is 569,792 bytes in size.

BACKGROUND

[0002] Macrophages are powerful modulators of the immune response and can generally adopt either a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. A precise balance of M1/M2 macrophages is important in resolving the body's response to disease and injury, and various diseases include dysregulated M1/M2 phenotypes. For example, macrophages in the tumor microenvironment (TME) are often biased toward an M2 phenotype that safeguards the tumor, while M1 macrophages in atherosclerotic tissue promote plaque progression.

[0003] Therefore, a need exists for establish a method to genetically control and/or maintain the M1/M2 polarization of engineered immune cells for cell therapies.

SUMMARY OF THE INVENTION

[0004] The present disclosure encompasses, among other things, compositions comprising modified immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells) comprising exogenous cytokines and methods of producing the same. The present

disclosure also encompasses, among other things, compositions comprising modified immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells) comprising fusion proteins and methods of producing the same.

[0005] The present disclosure provides a system for establishing genetic control over immune cell (e.g., stem cell, macrophage, monocyte, and/or dendritic cell) phenotype using cytokine-based signaling. The present disclosure provides, *inter alia*, co-expression of pro-inflammatory (M1) or anti-inflammatory (M2) promoting exogenous cytokines with a chimeric antigen receptor (CAR) in an immune cell (e.g., stem cell, macrophage, monocyte, and/or dendritic cell), which enables the immune cell to produce large quantities of the expressed exogenous cytokine. Additionally, co-expression of a pro-inflammatory (M1) promoting exogenous cytokine and a CAR in an immune cell (e.g., stem cell, macrophage, monocyte, and/or dendritic cell) enables the immune cell to "self-polarize" to an M1 phenotype. Similarly, co-expression of an anti-inflammatory (M2) promoting exogenous cytokine and a CAR in an immune cell (e.g., stem cell, macrophage, monocyte, and/or dendritic cell) enables the immune cell to "self-polarize" to an M2 phenotype.

[0006] The present disclosure also provides, *inter alia*, fusion proteins in which a pro-inflammatory (M1) or anti-inflammatory (M2) promoting cytokine is directly fused to one of its corresponding receptor subunits, such that the cytokine can intramolecularly bind its tethered receptor and induce downstream signaling. Unlike naturally occurring soluble cytokines, the tethered cytokines of the present disclosure are designed to only stimulate the modified immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells); direct fusion to the receptor can prevent cytokine diffusion from the cell membrane and can encourage rapid binding kinetics due to a high local concentration. This tethered cytokine-cytokine receptor fusion protein design may thereby provide a constitutive pro-inflammatory (M1) or anti-inflammatory (M2) promoting signal to the modified immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells), with minimized risk for cytotoxic effects on surrounding cells.

[0007] In one aspect, the present disclosure provides a modified immune cell comprising a fusion protein comprising a cytokine, a linker, and a cytokine receptor, wherein the modified immune cell is a stem cell, macrophage, monocyte, or dendritic cell and the cytokine binds the

cytokine receptor. In some embodiments, a fusion protein is membrane-bound. In some embodiments, a linker is a flexible linker. In some embodiments, a linker is a cleavable linker.

[0008] In some embodiments, a modified immune cell further comprises a chimeric antigen receptor (CAR).

[0009] In some embodiments, a fusion protein further comprises a signal peptide. In some embodiments, a fusion protein comprises, from N-terminus to C-terminus: a signal peptide, a cytokine, a linker, and a cytokine receptor. In some embodiments, a fusion protein comprises an amino acid sequence at least 80% identical to a sequence selected from Table 2a, Table 2b, Table 3a, Table 3b, Table 6, Table 8, or Table 9.

[0010] In another aspect, the present disclosure provides a modified immune cell comprising one or more nucleic acids encoding a fusion protein comprising a cytokine, a linker, and a cytokine receptor, wherein the modified immune cell is a stem cell, macrophage, monocyte or dendritic cell and the cytokine binds the cytokine receptor. In some embodiments, a fusion protein is membrane-bound. In some embodiments, a linker is a flexible linker. In some embodiments, a linker is a cleavable linker.

[0011] In some embodiments, a modified immune cell further comprises a chimeric antigen receptor (CAR).

[0012] In some embodiments, a fusion protein further comprises a signal peptide. In some embodiments, a fusion protein comprises, from N-terminus to C-terminus: a signal peptide, a cytokine, a linker, and a cytokine receptor. In some embodiments, one or more nucleic acids encoding a fusion protein comprise a sequence at least 80% identical to a sequence selected from Table 10. In some embodiments, one or more nucleic acids encoding a fusion protein comprise a sequence at least 80% identical to a sequence selected from Table 11a or 11b. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 4a, Table 4b, or Table 7. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 5a or Table 5b. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a signal peptide sequence selected from Table 8. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a linker sequence selected from Table 8.

[0013] In some embodiments, a signal peptide is or comprises a CD8a, IgG κ, PDGFR-β, Type I Interferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2 signal peptide.

[0014] In some embodiments, a cytokine is or comprises a pro-inflammatory cytokine. In some embodiments, a cytokine is or comprises an anti-inflammatory cytokine. In some embodiments, a cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, or GM-CSF. In some embodiments, a cytokine is or comprises IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β. In some embodiments, a cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β.

[0015] In some embodiments, a cytokine receptor is or comprises a pro-inflammatory cytokine receptor. In some embodiments, a cytokine receptor is or comprises an anti-inflammatory cytokine receptor. In some embodiments, a cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, or CSF2-Rβ. In some embodiments, a cytokine receptor is or comprises IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2. In some embodiments, a cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC,

IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2.

[0016] In some embodiments, a linker is or comprises a linker selected from a group consisting of: a $(G4S)_n$ linker, wherein n = 1-5 **(SEQ ID NO: 170)**, a Whitlow linker, and Linker 26.

[0017] In another aspect, the present disclosure provides a modified immune cell comprising a fusion protein comprising interleukin 10 (IL-10), a linker, and interleukin-10 receptor (IL10R). In another aspect, the present disclosure provides a modified immune cell comprising a fusion protein comprising interferon beta (IFNβ), a linker, and interferon-α/β receptor (IFNAR).

[0018] In some embodiments, a fusion protein is membrane-bound. In some embodiments, a linker is a flexible linker. In some embodiments, a linker is a cleavable linker.

[0019] In some embodiments, a modified immune cell further comprises a chimeric antigen receptor (CAR).

[0020] In another aspect, the present disclosure provides a pharmaceutical composition comprising a modified immune cell of the present disclosure. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[0021] In another aspect, the present disclosure provides a nucleic acid construct comprising one or more nucleic acids encoding a fusion protein comprising a cytokine and a cytokine receptor. In some embodiments, a nucleic acid construct further comprises one or more nucleic acids encoding a chimeric antigen receptor (CAR).

[0022] In another aspect, the present disclosure provides a pharmaceutical composition comprising a nucleic acid construct of the present disclosure. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[0023] In another aspect, the present disclosure provides a method of treating or preventing a disease or disorder in a subject, comprising delivering to the subject a therapeutically effective amount of a pharmaceutical composition of the present disclosure.

[0024] In another aspect, the present disclosure provides a method of modifying an immune cell, the method comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding a fusion protein comprising a cytokine, a linker, and a cytokine receptor. In some embodiments, a linker is a flexible linker. In some embodiments, a linker is a cleavable linker. In some embodiments, a nucleic acid construct further comprises one or more nucleic acids encoding a chimeric antigen receptor (CAR). In some embodiments, delivering comprises electroporation or transfection with DNA, mRNA, or chemically modified mRNA. In some embodiments, delivering comprises transduction with an adeno-associated viral (AAV) vector, an adenoviral vector, or a retroviral vector. In some embodiments, a retroviral vector comprises a lentiviral vector or a gammaretroviral vector. In some embodiments, a lentiviral vector is packaged with a Vpx protein. In some embodiments, an adenoviral vector comprises an Ad2 vector or an Ad5 vector. In some embodiments, an Ad5 vector comprises an Ad5f35 adenoviral vector. In some embodiments, delivery comprises transposon-based delivery or CRISPR-based targeted integration.

[0025] In another aspect, the present disclosure provides a modified immune cell comprising an exogenous cytokine and a chimeric antigen receptor (CAR), wherein the modified immune cell is a stem cell, macrophage, monocyte, or dendritic cell and the exogenous cytokine is or comprises a pro-inflammatory cytokine, an anti-inflammatory cytokine, or a chemoattractant chemokine. In some embodiments, an exogenous cytokine comprises a signal peptide. In some embodiments, an exogenous cytokine comprises an amino acid sequence at least 80% identical to a sequence selected from Table 2a, Table 2b, Table 6, or Table 8.

[0026] In another aspect, the present disclosure provides a modified immune cell comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR), wherein the modified immune cell is a stem cell, macrophage, monocyte or dendritic cell and the exogenous cytokine is or comprises a pro-inflammatory cytokine, an anti-inflammatory cytokine, or a chemoattractant chemokine. In some embodiments, an exogenous cytokine further comprises a signal peptide. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 4a, Table 4b, Table 7, or Table 11b. In some embodiments, one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 8.

[0027] In some embodiments, one or more nucleic acids encode a signal peptide. In some embodiments, a signal peptide is or comprises a CD8a, IgG κ, PDGFR-β, Type I Interferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2 signal peptide.

[0028] In some embodiments, an exogenous cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, CCL19, or CXCL12. In some embodiments, an exogenous cytokine is or comprises IFN-γ, IL-10, CCL19, or CXCL12.

[0029] In another aspect, the present disclosure provides a pharmaceutical composition comprising a modified immune cell of the present disclosure comprising an exogenous cytokine and a CAR. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[0030] In another aspect, the present disclosure provides a nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR).

[0031] In another aspect, the present disclosure provides a pharmaceutical composition comprising a nucleic acid construct of the present disclosure comprising one or more nucleic acids encoding an exogenous cytokine and a CAR. In some embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[0032] In another aspect, the present disclosure provides a method of treating or preventing a disease or disorder in a subject, comprising delivering to the subject a therapeutically effective amount of a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a modified immune cell of the present

disclosure comprising an exogenous cytokine and a CAR or a nucleic acid construct of the present disclosure comprising one or more nucleic acids encoding an exogenous cytokine and a CAR.

[0033] In another aspect, the present disclosure provides a method of modifying an immune cell, the method comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR). In some embodiments, the delivering comprises electroporation or transfection with DNA, mRNA, or chemically modified mRNA. In some embodiments, delivering comprises transduction with an adeno-associated viral (AAV) vector, an adenoviral vector, or a retroviral vector. In some embodiments, a retroviral vector comprises a lentiviral vector or a gammaretroviral vector. In some embodiments, a lentiviral vector is packaged with a Vpx protein. In some embodiments, an adenoviral vector comprises an Ad2 vector or an Ad5 vector. In some embodiments, an Ad5 vector comprises an Ad5f35 adenoviral vector. In some embodiments, delivery comprises transposon-based delivery or CRISPR-based targeted integration.

BRIEF DESCRIPTION OF THE DRAWING

[0034] The drawings are for illustration purposes only, not for limitation.

[0035] **Figure 1** shows exemplary fusion proteins comprising IFN-β and IFNAR1/2 and IL10 and IL10RA/B.

[0036] **Figure 2** shows exemplary fusion protein designs comprising a signal peptide, a cytokine, a linker and a cytokine receptor, wherein the cytokine binds the cytokine receptor. Figure discloses "(GGGGS)x" as SEQ ID NO: 175.

[0037] **Figure 3A** and **Figure 3B** show illustrations of an exemplary method of the present disclosure, comprising gene delivery of constructs encoding a fusion protein (and optionally a CAR, see **Figure 3B**) to an immune cell (e.g., a macrophage), dimerization of the fusion protein with an endogenous receptor and polarization of a macrophage to a pro-inflammatory (i.e., M1) state.

[0038] **Figure 4A** and **Figure 4B** show illustrations of an exemplary method of the present disclosure, comprising gene delivery of constructs encoding a fusion protein (and optionally a CAR, see Figure 4B) to an immune cell (e.g., a macrophage), dimerization of the fusion protein with an endogenous receptor and polarization of a macrophage to an anti-inflammatory (i.e., M2) state.

[0039] **Figure 5A** and **Figure 5B** show exemplary constructs comprising a signal peptide, a FLAG tag, a cytokine, a linker, a cytokine receptor, a P2A peptide and mCherry. In **Figure 5A**, an antibody binds the FLAG tag and in **Figure 5B**, an antibody binds the cytokine.

[0040] **Figure 6A** and **Figure 6B** show exemplary graphs illustrating viability of HEK293T cells (**Figure 6A**) and surface expression of fusion proteins in HEK293T cells (**Figure 6B**) transfected with plasmid DNA.

[0041] **Figure 7** shows exemplary graphs illustrating a correlation between detection of a FLAG tag by an antibody and mCherry expression in the IFNβ-IFNAR1 and IL4-IL13Rα groups.

[0042] **Figure 8** shows exemplary Western blots illustrating expression of the fusion proteins in HEK293T cells.

[0043] **Figure 9** shows an exemplary construct comprising a signal peptide, a FLAG tag, a cytokine, a linker, a cytokine receptor, a P2A peptide and mCherry. This figure also illustrates an antibody that binds the FLAG tag.

[0044] **Figure 10A** and **Figure 10B** show exemplary graphs illustrating viability of macrophages (**Figure 10A**) and surface expression of fusion proteins in macrophages (**Figure 10B**) transduced with VPX-Lentivirus comprising a fusion protein.

[0045] **Figure 11A** and **Figure 11B** show exemplary graphs illustrating viability, P2A-mCherry expression, and surface expression of fusion proteins in macrophages transduced with VPX-Lentivirus comprising a fusion protein.

[0046] **Figure 12A** and **Figure 12B** show exemplary graphs illustrating expression of pro-inflammatory (M1) and anti-inflammatory (M2) markers from macrophages that were transduced with VPX-Lentivirus comprising a fusion protein.

[0047] **Figure 13** shows an exemplary graph illustrating viability of macrophages after transfection with mRNA encoding cytokines and a CAR.

[0048] **Figure 14** shows an exemplary graph illustrating CAR expression in macrophages after transfection with mRNA encoding cytokines and a CAR.

[0049] **Figure 15** shows an exemplary graph illustrating IFN-γ levels from macrophages after transfection with mRNA encoding cytokines and a CAR.

[0050] **Figure 16** shows an exemplary graph illustrating IL-10 levels from macrophages after transfection with mRNA encoding cytokines and a CAR.

[0051] **Figure 17** shows an exemplary graph illustrating CCL19 levels from macrophages after transfection with mRNA encoding cytokines and a CAR.

[0052] **Figure 18** shows an exemplary graph illustrating CXCL12 levels from macrophages after transfection with mRNA encoding cytokines and a CAR.

[0053] **Figure 19** shows exemplary graphs illustrating levels of pro-inflammatory (M1) markers CD80 and CD86 from macrophages after transfection with mRNA encoding cytokines and a CAR.

[0054] **Figure 20** shows exemplary graphs illustrating levels of anti-inflammatory (M2) markers CD163 and CD206 from macrophages after transfection with mRNA encoding cytokines and a CAR.

DEFINITIONS

[0055] In order for the present invention to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the specification. The publications and other reference materials referenced herein to describe the background of the invention and to provide additional detail regarding its practice are hereby incorporated by reference.

[0056] The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0057] *Approximately or about:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1 %, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0058] *Activation:* As used herein, the term "activation" refers to the state of a cell, for example a monocyte, macrophage, or dendritic cell that has been sufficiently stimulated to induce detectable cellular proliferation or has been stimulated to exert its effector function. Activation can also be associated with induced cytokine production, phagocytosis, cell signaling, target cell killing, and/or antigen processing and presentation.

[0059] *Activated monocytes/macrophages/dendritic cells*: As used herein, the term "activated monocytes/macrophages/dendritic cells" refers to, among other things, monocyte/macrophage/dendritic cells that are undergoing cell division or exerting effector function. The term "activated monocytes/macrophages/dendritic cells" refers to, among others thing, cells that are performing an effector function or exerting any activity not seen in the resting state, including phagocytosis, cytokine secretion, proliferation, gene expression changes, metabolic changes, and other functions.

[0060] *Agent*: As used herein, the term "agent" (or "biological agent" or "therapeutic agent"), refers to a molecule that may be expressed, released, secreted or delivered to a target by a modified cell described herein. An agent includes, but is not limited to, a nucleic acid, an antibiotic, an anti-inflammatory agent, an antibody or fragments thereof, an antibody agent or fragments thereof, a growth factor, a cytokine, an enzyme, a protein (e.g., an RNAse inhibitor), a peptide, a fusion protein, a synthetic molecule, an organic molecule (e.g., a small molecule), a carbohydrate, a lipid, a hormone, a microsome, a derivative or a variation thereof, and any combinations thereof. An agent may bind any cell moiety, such as a receptor, an antigenic determinant, or other binding site present on a target or target cell. An agent may diffuse or be transported into a cell, where it may act intracellularly.

[0061] *Antibody*: As used herein, the term "antibody" refers to a polypeptide that includes canonical immunoglobulin sequence elements sufficient to confer specific binding to a particular target antigen. As is known in the art, intact antibodies as produced in nature are approximately 150 kD tetrameric agents comprising two identical heavy chain polypeptides (about 50 kD each) and two identical light chain polypeptides (about 25 kD each) that associate with each other into what is commonly referred to as a "Y-shaped" structure. Each heavy chain comprises at least four domains (each about 110 amino acids long) – an amino-terminal variable (VH) domain (located at the tips of the Y structure), followed by three constant domains: CH1, CH2, and the carboxy-terminal CH3 (located at the base of the Y's stem). A short region, known as the "switch", connects the heavy chain variable and constant regions. The "hinge" connects CH2 and CH3 domains to the rest of the antibody. Two disulfide bonds in this hinge region connect the two heavy chain polypeptides to one another in an intact antibody. Each light chain comprises two domains – an amino-terminal variable (VL) domain, followed by a carboxy-terminal constant (CL) domain, separated from one another by another "switch". Intact antibody tetramers comprise two heavy chain-light chain dimers in which the heavy and light chains are linked to one another by a single disulfide bond; two other disulfide bonds connect the heavy chain hinge regions to one another, so that the dimers are connected to one another and a tetramer is formed. Naturally-produced antibodies are also glycosylated, typically on the CH2 domain. Each domain in a natural antibody has a structure characterized by an "immunoglobulin fold" formed from two beta sheets (e.g., 3-, 4-, or 5-stranded sheets) packed against each other in a compressed antiparallel beta barrel. Each variable domain contains three hypervariable loops known as "complementarity determining regions" (CDR1, CDR2, and CDR3) and four somewhat invariant "framework" regions (FR1, FR2, FR3, and FR4). When natural antibodies fold, the FR regions form the beta sheets that provide the structural framework for the domains, and the CDR loop regions from both the heavy and light chains are brought together in three-dimensional space so that they create a single hypervariable antigen binding site located at the tip of the Y structure. The Fc region of naturally-occurring antibodies binds to elements of the complement system, and also to receptors on effector cells, including, for example, effector cells that mediate cytotoxicity. Affinity and/or other binding attributes of Fc regions for Fc receptors can be modulated through glycosylation or other modification. In some embodiments, antibodies produced and/or utilized in accordance with the present invention (e.g., as a component of a

CAR) include glycosylated Fc domains, including Fc domains with modified or engineered glycosylation. In some embodiments, any polypeptide or complex of polypeptides that includes sufficient immunoglobulin domain sequences as found in natural antibodies can be referred to and/or used as an "antibody", whether such polypeptide is naturally produced (e.g., generated by an organism reacting to an antigen), or produced by recombinant engineering, chemical synthesis, or other artificial system or methodology. In some embodiments, an antibody is polyclonal. In some embodiments, an antibody is monoclonal. In some embodiments, an antibody has constant region sequences that are characteristic of mouse, rabbit, primate, or human antibodies. In some embodiments, antibody sequence elements are humanized, primatized, chimeric, etc, as is known in the art. Moreover, the term "antibody", as used herein, can refer in appropriate embodiments (unless otherwise stated or clear from context) to any of the art-known or developed constructs or formats for utilizing antibody structural and functional features in alternative presentation. For example, in some embodiments, an antibody utilized in accordance with the present invention is in a format selected from, but not limited to, intact IgA, IgG, IgE or IgM antibodies; bi- or multi- specific antibodies (e.g., Zybodies®, etc); antibody fragments such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd' fragments, Fd fragments, and isolated CDRs or sets thereof; single chain Fvs; polypeptide-Fc fusions; single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof); cameloid antibodies; masked antibodies (e.g., Probodies®); Small Modular ImmunoPharmaceuticals ("SMIPs™"); single chain or Tandem diabodies (TandAb®); VHHs; Anticalins®; Nanobodies® minibodies; BiTE®s; ankyrin repeat proteins or DARPINs®; Avimers®; DARTs; TCR-like antibodies;, Adnectins®; Affilins®; Trans-bodies®; Affibodies®; TrimerX®; MicroProteins; Fynomers®, Centyrins®; and KALBITOR®s. In some embodiments, an antibody may lack a covalent modification (e.g., attachment of a glycan) that it would have if produced naturally. In some embodiments, an antibody may contain a covalent modification (e.g., attachment of a glycan, a payload [e.g., a detectable moiety, a therapeutic moiety, a catalytic moiety, etc], or other pendant group [e.g., poly-ethylene glycol, etc.].

[0062] *Antibody agent*: As used herein, the term "antibody agent" refers to an agent that specifically binds to a particular antigen. In some embodiments, the term encompasses any polypeptide or polypeptide complex that includes immunoglobulin structural elements sufficient to confer specific binding. Exemplary antibody agents include, but are not limited to monoclonal

antibodies or polyclonal antibodies. In some embodiments, an antibody agent may include one or more constant region sequences that are characteristic of mouse, rabbit, primate, or human antibodies. In some embodiments, an antibody agent may include one or more sequence elements are humanized, primatized, chimeric, etc., as is known in the art. In many embodiments, the term "antibody agent" is used to refer to one or more of the art-known or developed constructs or formats for utilizing antibody structural and functional features in alternative presentation. For example, in some embodiments, an antibody agent utilized in accordance with the present invention is in a format selected from, but not limited to, intact IgA, IgG, IgE or IgM antibodies; bi- or multi- specific antibodies (e.g., Zybodies®, etc); antibody fragments such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd' fragments, Fd fragments, and isolated CDRs or sets thereof; single chain Fvs; polypeptide-Fc fusions; single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof); cameloid antibodies; masked antibodies (e.g., Probodies®); Small Modular ImmunoPharmaceuticals ("SMIPsTM"); single chain or Tandem diabodies (TandAb®); VHHs; Anticalins®; Nanobodies® minibodies; BiTE®s; ankyrin repeat proteins or DARPINs®; Avimers®; DARTs; TCR-like antibodies;, Adnectins®; Affilins®; Trans-bodies®; Affibodies®; TrimerX®; MicroProteins; Fynomers®, Centyrins®; and KALBITOR®s. In some embodiments, an antibody agent may lack a covalent modification (e.g., attachment of a glycan) that it would have if produced naturally. In some embodiments, an antibody agent may contain a covalent modification (e.g., attachment of a glycan, a payload [e.g., a detectable moiety, a therapeutic moiety, a catalytic moiety, etc], or other pendant group [e.g., poly-ethylene glycol, etc.]. In many embodiments, an antibody agent is or comprises a polypeptide whose amino acid sequence includes one or more structural elements recognized by those skilled in the art as a complementarity determining region (CDR); in some embodiments an antibody agent is or comprises a polypeptide whose amino acid sequence includes at least one CDR (e.g., at least one heavy chain CDR and/or at least one light chain CDR) that is substantially identical to one found in a reference antibody. In some embodiments an included CDR is substantially identical to a reference CDR in that it is either identical in sequence or contains between 1-5 amino acid substitutions as compared with the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that it shows at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the

reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that it shows at least 96%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that at least one amino acid within the included CDR is deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that 1-5 amino acids within the included CDR are deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical to the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that at least one amino acid within the included CDR is substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that 1-5 amino acids within the included CDR are deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical to the reference CDR. In some embodiments, an antibody agent is or comprises a polypeptide whose amino acid sequence includes structural elements recognized by those skilled in the art as an immunoglobulin variable domain. In some embodiments, an antibody agent is a polypeptide protein having a binding domain which is homologous or largely homologous to an immunoglobulin-binding domain. In some embodiments, an antibody agent is not and/or does not comprise a polypeptide whose amino acid sequence includes structural elements recognized by those skilled in the art as an immunoglobulin variable domain. In some embodiments, an antibody agent may be or comprise a molecule or composition which does not include immunoglobulin structural elements (e.g., a receptor or other naturally occurring molecule which includes at least one antigen binding domain).

[0063] *Antibody fragment*: As used herein, the term "antibody fragment" refers to a portion of an intact antibody and refers to the antigenic determining variable regions of an intact antibody. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments, linear antibodies, scFv antibodies, and multispecific antibodies formed from antibody fragments and human and humanized versions thereof.

[0064] *Antibody heavy chain*: As used herein, the term "antibody heavy chain" refers to the larger of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations.

[0065] *Antibody light chain:* As used herein, the term "antibody light chain" refers to the smaller of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations.

[0066] *Synthetic antibody:* As used herein, the term "synthetic antibody" refers to an antibody that is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage as described herein. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using synthetic DNA or amino acid sequence technology which is available and well known in the art.

[0067] *Antigen:* As used herein, the term "antigen" or "Ag" refers to a molecule that is capable of provoking an immune response. This immune response may involve either antibody production, the activation of specific immunologically-competent cells, or both. A skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA that comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid.

[0068] *Anti-tumor effect:* As used herein, the term "anti-tumor effect" refers to a biological effect which can be manifested by a decrease in tumor volume, a decrease in the

number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies of the invention in prevention of the occurrence of a tumor in the first place.

[0069] *Autologous:* As used herein, the term "autologous" refers to any material derived from an individual to which it is later to be re-introduced into the same individual.

[0070] *Allogeneic:* As used herein, the term "allogeneic" refers to any material (e.g., a population of cells) derived from a different animal of the same species.

[0071] *Xenogenic:* As used herein, the term "xenogeneic" refers to any material (e.g., a population of cells) derived from an animal of a different species.

[0072] *Cancer:* As used herein, the term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers include but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. In certain embodiments, the cancer is medullary thyroid carcinoma.

[0073] *Conservative sequence modifications:* As used herein, the term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the binding characteristics of an antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody compatible with various embodiments by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which an amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine,

isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of an antibody can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for the ability to bind antigens using the functional assays described herein.

[0074] *Co-stimulatory ligand:* As used herein, the term "co-stimulatory ligand" refers to a molecule on an antigen presenting cell (e.g., an APC, dendritic cell, B cell, and the like) that specifically binds a cognate co-stimulatory molecule on a monocyte/macrophage/dendritic cell, thereby providing a signal which mediates a monocyte/macrophage/dendritic cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A co-stimulatory ligand can include, but is not limited to, CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), CD30L, CD40, CD70, CD83, HLA-G, MICA, MICB, HVEM, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, HVEM, an agonist or antibody that binds Toll ligand receptor and a ligand that specifically binds with B7-H3. A co-stimulatory ligand also encompasses, inter alia, an antibody that specifically binds with a co-stimulatory molecule present on a monocyte/macrophage/dendritic cell, such as, but not limited to, CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, and a ligand that specifically binds with CD83.

[0075] *Cytotoxic:* As used herein, the term "cytotoxic" or "cytotoxicity" refers to killing or damaging cells. In one embodiment, cytotoxicity of the metabolically enhanced cells is improved, e.g. increased cytolytic activity of macrophages.

[0076] *Effective amount*: As used herein, "effective amount" and "therapeutically effective amount" are interchangeable, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result or provides a manufacturing, therapeutic or prophylactic benefit. Such results may include, but are not limited to, anti-tumor activity as determined by any means suitable in the art.

[0077] *Effector function*: As used herein, "effector function" or "effector activity" refers to a specific activity carried out by an immune cell in response to stimulation of the immune cell. For example, an effector function of macrophages to engulf and digest cellular debris, foreign substances, microbes, cancer cells and other unhealthy cells by phagocytosis.

[0078] *Encoding:* As used herein, "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (i.e., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0079] *Endogenous:* As used herein "endogenous" refers to any material from or produced inside a particular organism, cell, tissue or system.

[0080] *Exogenous:* As used herein, the term "exogenous" refers to any material introduced from or produced outside a particular organism, cell, tissue or system.

[0081] *Expand:* As used herein, the term "expand" refers to increasing in number, as in an increase in the number of cells, for example, monocytes, macrophages, and/or dendritic cells. In one embodiment, monocytes, macrophages, or dendritic cells that are expanded ex vivo increase in number relative to the number originally present in a culture. In another embodiment, monocytes, macrophages, or dendritic cells that are expanded ex vivo increase in number relative to other cell types in a culture. In some embodiments, expansion may occur *in vivo*. The term "ex vivo," as used herein, refers to cells that have been removed from a living organism, (e.g., a human) and propagated outside the organism (e.g., in a culture dish, test tube, or bioreactor).

[0082] *Expression:* As used herein, the term "expression" of a nucleic acid sequence refers to generation of any gene product from a nucleic acid sequence. In some embodiments, a gene product can be a transcript. In some embodiments, a gene product can be a polypeptide. In some embodiments, expression of a nucleic acid sequence involves one or more of the following: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5' cap formation, and/or 3' end formation); (3)

translation of an RNA into a polypeptide or protein; and/or (4) post-translational modification of a polypeptide or protein.

[0083] *Expression vector:* As used herein, the term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, such as cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses).

[0084] *Fragment:* As used herein, the terms "fragment" or "portion" refers to a structure that includes a discrete portion of the whole, but lacks one or more moieties found in the whole structure. In some embodiments, a fragment consists of such a discrete portion. In some embodiments, a fragment consists of or comprises a characteristic structural element or moiety found in the whole. In some embodiments, a nucleotide fragment comprises or consists of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, or more monomeric units (e.g., nucleic acids) as found in the whole nucleotide. In some embodiments, a nucleotide fragment comprises or consists of at least about 5%, 10%, 15%, 20%, 25%, 30%, 25%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more of the monomeric units (e.g., residues) found in the whole nucleotide. The whole material or entity may in some embodiments be referred to as the "parent" of the whole.

[0085] *Homology:* As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, e.g., between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% similar (e.g., containing residues with related chemical

properties at corresponding positions). As will be understood by those skilled in the art, a variety of algorithms are available that permit comparison of sequences in order to determine their degree of homology, including by permitting gaps of designated length in one sequence relative to another when considering which residues "correspond" to one another in different sequences. Calculation of the percent homology between two nucleic acid sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-corresponding sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or substantially 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position; when a position in the first sequence is occupied by a similar nucleotide as the corresponding position in the second sequence, then the molecules are similar at that position. The percent homology between the two sequences is a function of the number of identical and similar positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences.

[0086] *Identity:* As used herein, the term "identity" refers to the subunit sequence identity between two polymeric molecules particularly between two amino acid molecules, such as, between two polypeptide molecules. When two amino acid sequences have the same residues at the same positions; e.g., if a position in each of two polypeptide molecules is occupied by an Arginine, then they are identical at that position. The identity or extent to which two amino acid sequences have the same residues at the same positions in an alignment is often expressed as a percentage. The identity between two amino acid sequences is a direct function of the number of matching or identical positions; e.g., if half (e.g., five positions in a polymer ten amino acids in length) of the positions in two sequences are identical, the two sequences are 50% identical; if 90% of the positions (e.g., 9 of 10), are matched or identical, the two amino acids sequences are 90% identical.

[0087] *Substantial identity:* As used herein, the term "substantial identity" refers to a comparison between amino acid or nucleic acid sequences. As will be appreciated by those of ordinary skill in the art, two sequences are generally considered to be "substantially identical" if they contain identical residues in corresponding positions. As is well known in this art, amino acid or nucleic acid sequences may be compared using any of a variety of algorithms, including those available in commercial computer programs such as BLASTN for nucleotide sequences and BLASTP, gapped BLAST, and PSI-BLAST for amino acid sequences. In some embodiments, two sequences are considered to be substantially identical if at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of their corresponding residues are identical over a relevant stretch of residues. In some embodiments, the relevant stretch is a complete sequence. In some embodiments, the relevant stretch is at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 or more residues. In the context of a CDR, reference to "substantial identity" typically refers to a CDR having an amino acid sequence at least 80%, preferably at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to that of a reference CDR.

[0088] *Immune cell*: As used herein, the term "immune cell," refers to a cell that is involved in an immune response, e.g., promotion of an immune response. Examples of immune cells include, but are not limited to, macrophages, monocytes, dendritic cells, neutrophils, eosinophils, mast cells, platelets, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, T-lymphocytes, or B-lymphocytes. A source of immune cells (e.g., macrophages, monocytes, or dendritic cells) can be obtained from a subject.

[0089] *Immune response:* As used herein the term "immune response" refers to a cellular and/or systemic response to an antigen that occurs when lymphocytes identify antigenic molecules as foreign and induce the formation of antibodies and/or activate lymphocytes to remove the antigen.

[0090] *Immunoglobulin:* As used herein, the term "immunoglobulin" or "Ig," refers to a class of proteins that function as antibodies. Antibodies expressed by B cells are sometimes referred to as a BCR (B cell receptor) or antigen receptor. The five members included in this class of proteins are IgA, IgG, IgM, IgD, and IgE. IgA is the primary antibody that is present in

body secretions, such as saliva, tears, breast milk, gastrointestinal secretions and mucus secretions of the respiratory and genitourinary tracts. IgG is the most common circulating antibody. IgM is the main immunoglobulin produced in the primary immune response in most subjects. It is the most efficient immunoglobulin in agglutination, complement fixation, and other antibody responses, and is important in defense against bacteria and viruses. IgD is an immunoglobulin that has no known antibody function, but may serve as an antigen receptor. IgE is an immunoglobulin that mediates immediate hypersensitivity by causing release of mediators from mast cells and basophils upon exposure to allergen.

[0091] *Isolated:* As used herein, the term "isolated" refers to something altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

[0092] *Modified:* As used herein, the term "modified" refers to a changed state or structure of a molecule or cell of the invention. Molecules may be modified in many ways, including chemically, structurally, and functionally. Cells may be modified through the introduction of nucleic acids.

[0093] *Modulating:* As used herein the term "modulating," refers to mediating a detectable increase or decrease in the level of a response and/or a change in the nature of a response in a subject compared with the level and/or nature of a response in the subject in the absence of a treatment or compound, and/or compared with the level and/or nature of a response in an otherwise identical but untreated subject. The term encompasses perturbing and/or affecting a native signal or response thereby mediating a beneficial therapeutic response in a subject, preferably, a human.

[0094] *Nucleic acid*: As used herein, the term "nucleic acid" refers to a polymer of at least three nucleotides. In some embodiments, a nucleic acid comprises DNA. In some embodiments, a nucleic acid comprises RNA. In some embodiments, a nucleic acid is single stranded. In some embodiments, a nucleic acid is double stranded. In some embodiments, a nucleic acid comprises both single and double stranded portions. In some embodiments, a

nucleic acid comprises a backbone that comprises one or more phosphodiester linkages. In some embodiments, a nucleic acid comprises a backbone that comprises both phosphodiester and non-phosphodiester linkages. For example, in some embodiments, a nucleic acid may comprise a backbone that comprises one or more phosphorothioate or 5'-N-phosphoramidite linkages and/or one or more peptide bonds, e.g., as in a "peptide nucleic acid". In some embodiments, a nucleic acid comprises one or more, or all, natural residues (*e.g.,* adenine, cytosine, deoxyadenosine, deoxycytidine, deoxyguanosine, deoxythymidine, guanine, thymine, uracil). In some embodiments, a nucleic acid comprises one or more, or all, non-natural residues. In some embodiments, a non-natural residue comprises a nucleoside analog (e.g., 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3 -methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5 -propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, 0(6)-methylguanine, 2-thiocytidine, methylated bases, intercalated bases, and combinations thereof). In some embodiments, a non-natural residue comprises one or more modified sugars (e.g., 2'-fluororibose, ribose, 2'-deoxyribose, arabinose, and hexose) as compared to those in natural residues. In some embodiments, a nucleic acid has a nucleotide sequence that encodes a functional gene product such as an RNA or polypeptide. In some embodiments, a nucleic acid has a nucleotide sequence that comprises one or more introns. In some embodiments, a nucleic acid may be prepared by isolation from a natural source, enzymatic synthesis (e.g., by polymerization based on a complementary template, e.g., *in vivo* or *in vitro*, reproduction in a recombinant cell or system, or chemical synthesis. In some embodiments, a nucleic acid is at least 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 20, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 or more residues long.

[0095] *Operably linked:* As used herein, the term "operably linked" refers to functional linkage between, for example, a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked

to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame.

[0096] *Overexpressed tumor antigen:* As used herein, the term "overexpressed" tumor antigen or "overexpression" of a tumor antigen refers to an abnormal level of expression of a tumor antigen in a cell from a disease area like a solid tumor within a specific tissue or organ of the patient relative to the level of expression in a normal cell from that tissue or organ. Patients having solid tumors or a hematological malignancy characterized by overexpression of the tumor antigen can be determined by standard assays known in the art.

[0097] *Polynucleotide:* As used herein, the term "polynucleotide" refers to a chain of nucleotides. Furthermore, nucleic acids are polymers of nucleotides. Thus, nucleic acids and polynucleotides as used herein are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric "nucleotides." The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein polynucleotides include, but are not limited to, all nucleic acid sequences which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant library or a cell genome, using ordinary cloning technology and PCR™, and the like, and by synthetic means.

[0098] *Polypeptide:* As used herein, the term "polypeptide" refers to any polymeric chain of residues (e.g., amino acids) that are typically linked by peptide bonds. In some embodiments, a polypeptide has an amino acid sequence that occurs in nature. In some embodiments, a polypeptide has an amino acid sequence that does not occur in nature. In some embodiments, a polypeptide has an amino acid sequence that is engineered in that it is designed and/or produced through action of the hand of man. In some embodiments, a polypeptide may comprise or consist of natural amino acids, non-natural amino acids, or both. In some embodiments, a polypeptide may comprise or consist of only natural amino acids or only non-natural amino acids. In some embodiments, a polypeptide may comprise D-amino acids, L-amino acids, or both. In some embodiments, a polypeptide may comprise only D-amino acids. In some embodiments, a polypeptide may comprise only L-amino acids. In some embodiments, a polypeptide may include one or more pendant groups or other modifications, e.g., modifying or

attached to one or more amino acid side chains, at the polypeptide's N-terminus, at the polypeptide's C-terminus, or any combination thereof. In some embodiments, such pendant groups or modifications may be selected from the group consisting of acetylation, amidation, lipidation, methylation, pegylation, etc., including combinations thereof. In some embodiments, a polypeptide may be cyclic, and/or may comprise a cyclic portion. In some embodiments, a polypeptide is not cyclic and/or does not comprise any cyclic portion. In some embodiments, a polypeptide is linear. In some embodiments, a polypeptide may be or comprise a stapled polypeptide. In some embodiments, the term "polypeptide" may be appended to a name of a reference polypeptide, activity, or structure; in such instances it is used herein to refer to polypeptides that share the relevant activity or structure and thus can be considered to be members of the same class or family of polypeptides. For each such class, the present specification provides and/or those skilled in the art will be aware of exemplary polypeptides within the class whose amino acid sequences and/or functions are known; in some embodiments, such exemplary polypeptides are reference polypeptides for the polypeptide class or family. In some embodiments, a member of a polypeptide class or family shows significant sequence homology or identity with, shares a common sequence motif (e.g., a characteristic sequence element) with, and/or shares a common activity (in some embodiments at a comparable level or within a designated range) with a reference polypeptide of the class; in some embodiments with all polypeptides within the class). For example, in some embodiments, a member polypeptide shows an overall degree of sequence homology or identity with a reference polypeptide that is at least about 30-40%, and is often greater than about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more and/or includes at least one region (e.g., a conserved region that may in some embodiments be or comprise a characteristic sequence element) that shows very high sequence identity, often greater than 90% or even 95%, 96%, 97%, 98%, or 99%. Such a conserved region usually encompasses at least 3-4 and often up to 20 or more amino acids; in some embodiments, a conserved region encompasses at least one stretch of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous amino acids. In some embodiments, a useful polypeptide may comprise or consist of a fragment of a parent polypeptide. In some embodiments, a useful polypeptide as may comprise or consist of a plurality of fragments, each of which is found in the same parent polypeptide in a different spatial arrangement relative to one another than is found in the polypeptide of interest (e.g.,

fragments that are directly linked in the parent may be spatially separated in the polypeptide of interest or vice versa, and/or fragments may be present in a different order in the polypeptide of interest than in the parent), so that the polypeptide of interest is a derivative of its parent polypeptide.

[0099] *Protein:* As used herein, the term "protein" refers to a polypeptide (i.e., a string of at least two amino acids linked to one another by peptide bonds). Proteins may include moieties other than amino acids (*e.g.*, may be glycoproteins, proteoglycans, etc.) and/or may be otherwise processed or modified. Those of ordinary skill in the art will appreciate that a "protein" can be a complete polypeptide chain as produced by a cell (with or without a signal sequence), or can be a characteristic portion thereof. Those of ordinary skill will appreciate that a protein can sometimes include more than one polypeptide chain, for example linked by one or more disulfide bonds or associated by other means. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful modifications include, e.g., terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0100] *Signal transduction pathway:* As used herein, the term "signal transduction pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase "cell surface receptor" includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the plasma membrane of a cell.

[0101] *Single chain antibodies:* As used herein, the term "single chain antibodies" refers to antibodies formed by recombinant DNA techniques in which immunoglobulin heavy and light chain fragments are linked to the Fv region via an engineered span of amino acids. Various methods of generating single chain antibodies are known, including those described in U.S. Pat.

No. 4,694,778; Bird (1988) Science 242:423-442; Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883; Ward et al. (1989) Nature 334:54454; Skerra et al. (1988) Science 242:1038-1041.

[0102] *Specifically binds:* As used herein, the term "specifically binds," with respect to an antigen binding domain, such as an antibody agent, refers to an antigen binding domain or antibody agent which recognizes a specific antigen, but does not substantially recognize or bind other molecules in a sample. For example, an antigen binding domain or antibody agent that specifically binds to an antigen from one species may also bind to that antigen from one or more species. But, such cross-species reactivity does not itself alter the classification of an antigen binding domain or antibody agent as specific. In another example, an antigen binding domain or antibody agent that specifically binds to an antigen may also bind to different allelic forms of the antigen. However, such cross reactivity does not itself alter the classification of an antigen binding domain or antibody agent as specific. In some instances, the terms "specific binding" or "specifically binding," can be used in reference to the interaction of an antigen binding domain or antibody agent, a protein, or a peptide with a second chemical species, to mean that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the chemical species; for example, an antigen binding domain or antibody agent recognizes and binds to a specific protein structure rather than to proteins generally. If an antigen binding domain or antibody agent is specific for epitope "A", the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled "A" and the antigen binding domain or antibody agent, will reduce the amount of labeled A bound to the antibody.

[0103] *Stimulation:* As used herein, the term "stimulation," refers to a primary response induced by binding of a stimulatory molecule (e.g., an FcR complex, a TLR complex, or a TCR/CD3 complex), for example, with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via Fc receptor machinery or via a synthetic CAR. Stimulation can mediate altered expression of certain molecules, such as downregulation of TGF-beta, and/or reorganization of cytoskeletal structures, and the like. As used herein, the term "stimulatory molecule," refers to a molecule of a monocyte, macrophage, or dendritic cell that specifically binds with a cognate stimulatory ligand present on an antigen

presenting cell. In some embodiments, a stimulatory molecule comprises an FcR extracellular domain comprising a CD64 (FcγRI), CD32a (FcγRIIa), CD32b (FcγRIIb), CD32c, CD16a (FcγRIIIa), CD16b (FcγRIIIb), FcεRI, FcεRII, FcαRI (CD89) or CD40 domain. In some embodiments, a stimulatory molecule comprises a TLR extracellular domain comprising a TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, or TLR9 domain. As used herein, the term "stimulatory ligand," refers to a ligand that when present on an antigen presenting cell (e.g., an aAPC, a macrophage, a dendritic cell, a B-cell, and the like) or tumor cell can specifically bind with a cognate binding partner (referred to herein as a "stimulatory molecule") on a monocyte, macrophage, or dendritic cell thereby mediating a response by the immune cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands are well-known in the art and encompass, *inter alia*, Toll-like receptor (TLR) ligand, an anti-toll-like receptor antibody, an agonist, and an antibody for a monocyte/macrophage receptor. In addition, cytokines, such as interferon-gamma, are potent stimulants of macrophages.

[0104] *Subject:* As used herein, the term "subject" refers to an organism, for example, a mammal (e.g., a human, a non-human mammal, a non-human primate, a primate, a laboratory animal, a mouse, a rat, a hamster, a gerbil, a cat, or a dog). In some embodiments a human subject is an adult, adolescent, or pediatric subject. In some embodiments, a subject is suffering from a disease, disorder or condition, e.g., a disease, disorder, or condition that can be treated as provided herein, e.g., a cancer or a tumor listed herein. In some embodiments, a subject is susceptible to a disease, disorder, or condition; in some embodiments, a susceptible subject is predisposed to and/or shows an increased risk (as compared to the average risk observed in a reference subject or population) of developing the disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms of a disease, disorder, or condition. In some embodiments, a subject does not display a particular symptom (e.g., clinical manifestation of disease) or characteristic of a disease, disorder, or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0105] *Substantially purified:* As used herein, the term "substantially purified", for example as applied to a cell, refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some embodiments, the cells are cultured *in vitro*. In other embodiments, the cells are not cultured *in vitro*.

[0106] *Target:* As used herein, the term "target" refers to a cell, tissue, organ, or site within the body that is the subject of provided methods, systems, and /or compositions, for example, a cell, tissue, organ or site within a body that is in need of treatment or is preferentially bound by, for example, an antibody (or fragment thereof) or a CAR.

[0107] *Target site:* As used herein, the term "target site" or "target sequence" refers to a genomic nucleic acid sequence that defines a portion of a nucleic acid to which a binding molecule may specifically bind under conditions sufficient for binding to occur.

[0108] *T cell receptor:* As used herein, the term "T cell receptor" or "TCR" refers to a complex of membrane proteins that participate in the activation of T cells in response to the presentation of antigen. A TCR is responsible for recognizing antigens bound to major histocompatibility complex molecules. A TCR comprises a heterodimer of an alpha (a) and beta (β) chain, although in some cells the TCR comprises gamma and delta (γ/δ) chains. TCRs may exist in alpha/beta and gamma/delta forms, which are structurally similar but have distinct anatomical locations and functions. Each chain comprises two extracellular domains, a variable and constant domain. In some embodiments, a TCR may be modified on any cell comprising a TCR, including, for example, a helper T cell, a cytotoxic T cell, a memory T cell, regulatory T cell, natural killer T cell, and gamma delta T cell.

[0109] *Therapeutic:* As used herein, the term "therapeutic" refers to a treatment and/or prophylaxis. A therapeutic effect is obtained by suppression, remission, or eradication of a disease state.

[0110] *Transfected:* As used herein, the term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid is transferred or introduced

into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

[0111] *Treat:* As used herein, the term "treat," "treatment," or "treating" refers to partial or complete alleviation, amelioration, delay of onset of, inhibition, prevention, relief, and/or reduction in incidence and/or severity of one or more symptoms or features of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who does not exhibit signs or features of a disease, disorder, and/or condition (e.g., may be prophylactic). In some embodiments, treatment may be administered to a subject who exhibits only early or mild signs or features of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits established, severe, and/or late-stage signs of the disease, disorder, or condition. In some embodiments, treating may comprise administering to an immune cell (e.g., a monocyte, macrophage, or dendritic cell) or contacting an immune cell with a modulator of a pathway activated by *in vitro* transcribed mRNA.

[0112] *Tumor:* As used herein, the term "tumor" refers to an abnormal growth of cells or tissue. In some embodiments, a tumor may comprise cells that are precancerous (*e.g.*, benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. In some embodiments, a tumor is associated with, or is a manifestation of, a cancer. In some embodiments, a tumor may be a disperse tumor or a liquid tumor. In some embodiments, a tumor may be a solid tumor.

[0113] *Vector:* As used herein, the term "vector" refers to a composition of matter that comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

[0114] Throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

DETAILED DESCIPTION

[0115] Macrophages are powerful modulators of the immune response and can generally adopt either a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. A precise balance of M1/M2 macrophages is important in the body's response to disease and injury, and various diseases include dysregulated M1/M2 phenotypes. For example, macrophages in the tumor microenvironment (TME) are often biased toward an M2 phenotype that safeguards the tumor, while M1 macrophages in atherosclerotic tissue typically promote plaque progression. Methods that allow external control over macrophage phenotype are thus promising therapeutic strategies, whether by repolarizing existing macrophages or by delivering macrophages of a desired phenotype (e.g. the delivery of M1 macrophages to the TME or M2 macrophages to atherosclerotic tissue).

[0116] Natural systems use cytokines as potent regulators of M1/M2 phenotype, and thus manipulated cytokine signaling networks represent an appealing system for engineering macrophages. However, cytokines have pleiotropic effects on various immune cells, creating the challenges of avoiding off-target signaling and exclusively activating macrophages of interest. Furthermore, uncontrolled cytokine expression can lead to cytokine release syndrome and other adverse side effects. In order to control an immune cell (e.g., macrophage, monocyte, or dendritic cell) phenotype by harnessing endogenous cytokine signaling pathways, an ideal technology would (i) specify a desired M1/M2 phenotype, (ii) maintain this phenotype in a

disease microenvironment, and (iii) have minimal cytotoxic off-target effects. The present disclosure provides, *inter alia*, such technology.

Immune Cells

[0117] The present disclosure, among other things, provides modified immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) comprising an exogenous cytokine as described herein and a chimeric antigen receptor (CAR) as described herein. Accordingly, in some embodiments, at least one CAR comprises: (a) an extracellular domain (e.g., an extracellular domain as described herein), (b) a transmembrane domain (e.g., a transmembrane domain as described herein), and (c) an intracellular domain (e.g., an intracellular domain as described herein).

[0118] The present disclosure, among other things, also provides modified immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) comprising at least one fusion protein as described herein. Accordingly, in some embodiments, an immune cell comprising fusion protein comprises: a cytokine ((e.g., a cytokine as described herein), a linker (e.g., a linker as described herein), and a cytokine receptor (e.g., a cytokine receptor as described herein), wherein the cytokine binds the cytokine receptor (see **Figures 3A** and **4A**). In some embodiments, an immune cell further comprises at least one chimeric antigen receptor (CAR) (see **Figures 3B** and **4B**). Accordingly, in some embodiments, at least one CAR comprises: (a) an extracellular domain (e.g., an extracellular domain as described herein), (b) a transmembrane domain (e.g., a transmembrane domain as described herein), and (c) an intracellular domain (e.g., an intracellular domain as described herein).

[0119] In some embodiments, a population of immune cells as described herein comprises stem cells, monocytes, macrophages, dendritic cells, and/or precursors thereof. In some embodiments, a population of immune cells comprises a substantially purified population of stem cells, monocytes, macrophages, or dendritic cells, or a cell line.

[0120] In some embodiments, an immune cell is activated, e.g., an immune cell exhibits increased cytokine production, chemokine production, phagocytosis, cell signaling, target cell killing, and/or antigen presentation, e.g., relative to an inactive cell. In some embodiments, an

activated immune cell exhibits changes in gene expression, e.g., an induction of pro-inflammatory gene expression (e.g., one, two, three, four, five, six, or seven of TNF, IL-12, IFN, GM-CSF, G-CSF, M-CSF, or IL-1), e.g., relative to an inactive cell. In some embodiments, an activated immune cell exhibits changes in gene expression, e.g., an induction of anti-inflammatory gene expression, e.g., relative to an inactive cell. In certain embodiments, activated immune cells are undergoing cell division. In some embodiments, targeted effector activity of an immune cell is enhanced by inhibition of CD47 and/or SIRPα activity. CD47 and/or SIRPα activity may be inhibited by treating an immune cell with an anti-CD47 or anti-SIRPα antibody or by any method known to those skilled in the art.

[0121] In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) are obtained (e.g., isolated) from a subject. Immune cells may be autologous or sourced from allogeneic or universal donors. Cells can be obtained from a number of sources including peripheral blood mononuclear cells, bone marrow, lymph node tissue, spleen tissue, umbilical cord, tumors, and/or induced pluripotent stem cells, such as embryonic stem cells (ESCs). In certain embodiments, cells can be obtained from a unit of blood collected from a subject using any number of separation techniques known to a skilled artisan, such as Ficoll separation. In some embodiments, cells from circulating blood of a subject are obtained by apheresis or leukapheresis. Cells collected by apheresis may be washed to remove a plasma fraction and resuspended in a variety of buffers (e.g., phosphate buffered saline (PBS)) or culture media). In some embodiments, enrichment of immune cells (e.g. monocytes) comprises plastic adherence. In some embodiments, following enrichment, differentiation of immune cells (e.g. monocytes) comprises stimulation with GM-CSF. In some embodiments, a composition comprising blood cells (e.g., monocytes, lymphocytes, platelets, plasma, and/or red blood cells), such as a leukapheresis composition (e.g., a leukopak) is used for enrichment. In some embodiments, a leukapheresis composition (e.g., a leukopak) comprises a sample from a healthy human donor. In certain embodiments, apheresis of immune cells (e.g. monocytes) is followed by mobilization with GM-CSF. In certain embodiments, selection of immune cells (e.g., monocytes) comprises CD14 positive selection using microbeads (e.g., MACS® MicroBeads on a CliniMACS Prodigy device). In some embodiments, an immune cell precursor (e.g., precursors to macrophages, monocytes, or dendritic cells including, but not limited to induced pluripotent stem cells, or iPSCs) is used in compositions and methods described herein. Immune

cell precursors may be differentiated *in vivo* or *ex vivo* into immune cells. Non-limiting examples of precursor immune cells include hematopoietic stem cells, common myeloid progenitors, myeloblasts, monoblasts, promonocytes, or intermediates thereof. For example, induced pluripotent stem cells may be used to generate monocytes, macrophages, and/or dendritic cells. Induced pluripotent stem cells (iPSCs) may be derived from normal human tissue, such as peripheral blood, fibroblasts, skin, keratinocytes, or renal epithelial cells. Autologous, allogeneic, or universal donor iPSCs could be differentiated toward a myeloid lineage (e.g., a monocyte, macrophage, dendritic cell, or precursor thereof).

[0122] Immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein can be isolated from peripheral blood, for example, by lysing red blood cells and depleting lymphocytes and red blood cells, such as by centrifugation through a PERCOLL™ gradient. Alternatively, immune cells can be isolated from umbilical cord tissue. A specific subpopulation of immune cells can be further isolated by positive or negative selection techniques. In some embodiments, immune cells can be depleted of cells expressing certain antigens, including, but not limited to, CD34, CD3, CD4, CD8, CD56, CD66b, CD19, or CD20. In some embodiments, enrichment of an immune cell population, for example, by negative selection can be accomplished using a combination of antibodies directed to surface markers unique to the negatively selected cells. By way of non-limiting example, cell selection can also comprise negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on negatively selected cells.

[0123] During isolation of a desired population of immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein by positive or negative selection, immune cell concentration and surface (e.g., particles, such as beads) can be varied. It may be desirable to significantly decrease volume in which beads and cells are mixed together to ensure maximum contact area of cells and beads.

[0124] In some embodiments, prior to administration, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein (e.g., comprising an exogenous cytokine described herein or a fusion protein described herein) are treated with a pro-inflammatory agent. In some embodiments, treatment with a pro-inflammatory agent increases anti-tumor activity of immune cells described herein. In some embodiments, treatment with a

pro-inflammatory agent promotes a pro-inflammatory (i.e., M1) phenotype (e.g., a switch from an anti-inflammatory (M2) to a pro-inflammatory (M1) phenotype) in immune cells described herein. In some embodiments, a pro-inflammatory agent comprises or is a CD40 agonist (e.g., CD40L). In some embodiments, a pro-inflammatory agent comprises or is a 41BB-ligand agonist (e.g., 4-1BB).

[0125] In some embodiments, prior to administration, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein (e.g., comprising an exogenous cytokine described herein or a fusion protein described herein) are treated with an anti-inflammatory agent. In some embodiments, treatment with an anti-inflammatory agent increases anti-inflammatory activity of immune cells described herein. In some embodiments, treatment with an anti-inflammatory agent promotes an anti-inflammatory (i.e., M2) phenotype (e.g., a switch from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype) in immune cells described herein. In some embodiments, an anti-inflammatory agent comprises or is an IL-10 agonist. In some embodiments, an anti-inflammatory agent comprises or is a TGFβ agonist.

[0126] In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein (e.g., comprising an exogenous cytokine described herein or a fusion protein described herein) are administered to a subject in combination with a pro-inflammatory agent. In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein (e.g., comprising an exogenous cytokine described herein or a fusion protein described herein) are administered to a subject substantially simultaneously, before, or after a pro-inflammatory agent. In some embodiments, administration with a pro-inflammatory agent increases anti-tumor activity of immune cells described herein. In some embodiments, administration with a pro-inflammatory agent promotes a pro-inflammatory (i.e., M1) phenotype (e.g., a switch from an anti-inflammatory (M2) to pro-inflammatory (M1) phenotype) in immune cells described herein. In some embodiments, a pro-inflammatory agent comprises or is a CD40 agonist (e.g., CD40L). In some embodiments, a pro-inflammatory agent comprises or is a 41BB-ligand agonists (e.g., 4-1BB).

Macrophages

[0127] Macrophages are immune cells specialized for detection, phagocytosis, and destruction of target cells, such as pathogens or tumor cells. Macrophages are potent effectors of the innate immune system and are capable of at least three distinct anti-tumor functions: 1) phagocytosis of dead and dying cells, microorganisms, cancer cells, cellular debris, or other foreign substances; 2) cytotoxicity against tumor cells; and 3) presentation of tumor antigens to orchestrate an adaptive anti-tumor immune response.

[0128] Accumulating evidence suggests that macrophages are abundant in the tumor microenvironment of numerous cancers and can adopt a number of phenotypes that are collectively referred to as tumor-associated macrophages (TAMs). The immunosuppressive nature of the tumor microenvironment typically results in more M2-like TAMs, which further contribute to the general suppression of anti-tumor immune responses. Recent studies, however, have identified that TAMs are able to be "reprogrammed" via pro-inflammatory signals, and that the switch from a M2 phenotype to a more M1 phenotype is associated with productive anti-tumor immune responses. Inducing endogenous TAMs to switch to M1-type cells and engineering macrophages that cannot be subverted into M2 would greatly enhance anti-tumor immunotherapy and represent a significant advance in the field.

[0129] In some embodiments, a macrophage comprises or is an undifferentiated or M0 macrophage. In certain embodiments, a macrophage comprises or expresses one, two, three, four, five, or six of CD14, CD16, CD64, CD68, CD71, or CCR5. Exposure to various stimuli can induce M0 macrophages to polarize into several distinct populations, which may be identified by macrophage phenotype markers, cytokine production, and/or chemokine secretion.

[0130] In some embodiments, a macrophage comprises or is a polarized macrophage. Under classical conditions of activation, M0 macrophages can be exposed to pro-inflammatory signals, such as LPS, IFNγ, and GM-CSF, and polarize into pro-inflammatory (i.e., M1) macrophages. Generally, pro-inflammatory (M1) macrophages are associated with pro-inflammatory immune responses, such as Th1 and Th17 T cell responses. Exposure to other stimuli can polarize macrophages into a diverse group of "alternatively activated" or anti-inflammatory (i.e., M2) macrophages.

[0131] In some embodiments, a macrophage comprises or is a pro-inflammatory (M1) macrophage. In some embodiments, a macrophage expresses one or more markers of pro-inflammatory (M1) macrophages (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 of CD86, CD80, MHC II, IL-1R, TLR2, TLR4, iNOS, SOCS3, CD83, PD-L1, CD69, MHC I, CD64, CD32, CD16, IL1R, a IFIT family member, or an ISG family member).

[0132] In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein secretes relatively high levels of one or more inflammatory cytokines (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 of IL-1, TNF, IL-12, IL-18, IL-23, IFNα, IFNβ, IFNγ, IL-2, IL-6, IL-8, or IL33) or chemokines (e.g., one or both of CC or CXC chemokines) (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 of the CXC chemokines; e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 of the CC chemokines; eg., one of the CX3C chemokines, e.g., one or both of the C chemokines), e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein stimulates an immune response and/or inflammation, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein.

[0133] In some embodiments, a macrophage comprises or is an anti-inflammatory (M2) macrophage (e.g., an M2a, M2b, M2c, and M2d macrophage). An M2a macrophage can be induced by IL-4, IL-13, and/or fungal infection. An M2b macrophage can be induced by IL-1R ligands, an immune complex, and/or LPS. An M2c macrophage can be induced by IL-10 and/or TGFβ. An M2d macrophage can be induced by IL-6 and/or adenosine. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein decreases an immune response in a subject, e.g., relative to a macrophage without an exogenous cytokine described herein or a fusion protein as described herein. In some embodiments, a macrophage expresses one or more markers of anti-inflammatory (M2) macrophages (e.g., one, two, or three of CD206, CD163, or CD209). In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased secretion of

one or more anti-inflammatory cytokines (e.g., one or both of IL-10 or TGFβ), e.g., relative to a macrophage without an exogenous cytokine described as herein or a fusion protein as described herein.

[0134] In some embodiments, a macrophage comprises at least one upregulated pro-inflammatory (M1) marker and/or at least one downregulated anti-inflammatory (M2) marker as compared to a control macrophage that does not comprise an exogenous cytokine as provided herein or a fusion protein as provided herein and/or the same macrophage before delivery of an exogenous cytokine described herein or a fusion protein as described herein. In some embodiments, at least one pro-inflammatory (M1) marker (e.g., HLA DR, CD86, CD80, PD-L1, CD83, CD69, MHC I, CD64, CD32, CD16, IL1R, an IFIT family member, and/or an ISG family member) is upregulated in a macrophage. In some embodiments, at least one anti-inflammatory (M2) marker (e.g., CD206, CD163, and/or CD209) is downregulated in a macrophage.

[0135] In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased phagocytosis, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased cytotoxicity against a tumor cell, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased tumor antigen presentation (e.g., post-phagocytosis presentation) and/or increased antigen processing, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased tumor killing (e.g., by phagocytosis, lysis, apoptosis, or production of tumor killing cytokines (e.g., TNFα), e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein.

[0136] In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one

or both of increased expression of one or more genes typically associated with increased effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion) (e.g., CD80, CD86, MHC-I, MHC-II, CD40, 41BBL, TNF, IFN-α, IFN-β, IFN-γ, IL2, IL12, IL6, IL8, IL1b, and/or CXCL12) or decreased expression of one or more genes typically associated with decreased effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion) (e.g., CD163, CD206, TGFβ, IL-10, and/or IL4), e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased production of ROS, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits metabolic reprogramming (e.g., of an interferon signaling pathway, TH1 pathway, PTEN signaling, PI3K signaling, MTOR signaling, TLR signaling, CD40 signaling, 41BB signaling, 41BBL signaling, macrophage maturation signaling, dendritic cell maturation signaling, CD3-zeta signaling, FcR γ signaling, CD64 signaling, CD32a signaling, CD32c signaling, CD16a signaling, TLR1 signaling, TLR2 signaling, TLR3 signaling, TLR4 signaling, TLR5 signaling, TLR6 signaling, TLR7 signaling, TLR8 signaling, TLR9 signaling, ALK signaling, AXL signaling, DDR2 signaling, EGFR signaling, EphA1 signaling, INSR signaling, cMET signaling, MUSK signaling, PDGFR signaling, PTK7 signaling, RET signaling, ROR1 signaling, ROS1 signaling, RYK signaling, TIE2 signaling, TRK signaling, VEGFR signaling, CD40 signaling, CD19 signaling, CD20 signaling, 41BB signaling, CD28 signaling, OX40 signaling, GITR signaling, TREM-1 signaling, TREM-2 signaling, DAP12 signaling, MR signaling, ICOS signaling, MyD88 signaling, V/I/LxYxxL/V signaling, SIRPα signaling, CD45 signaling, Siglec-10 signaling, PD1 signaling, SHP-1 signaling, SHP-2 signaling, KIR-2DL signaling, KIR-3DL signaling, NKG2A signaling, CD170 signaling, CD33 signaling, BTLA signaling, CD32b signaling, SIRPβ signaling, CD22 signaling, PIR-B signaling, and/or LILRB1 signaling), e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell

survival mechanisms, e.g., relative to a macrophage without an exogenous cytokine described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell death mechanisms, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one, two, three, four, or five of increased resistance to phagocytic checkpoints, increased expression of chemokine receptors to aid in trafficking, increased expression of chemokines to recruit other immune cells, increased expression of ECM degrading enzymes (e.g., MMPs to degrade tumor ECM and/or exhibit anti fibrotic activity), and/or increased proliferation, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein and at least one CAR as described herein exhibits one, two, three, or four of improved duration of exogenous cytokine expression, improved stability of the CAR on the cell surface, increased level of exogenous cytokine expression, and/or decreased background activity of the exogenous cytokine, e.g., relative to a macrophage without an exogenous cytokine as described herein. In some embodiments, a macrophage comprising or expressing at least one fusion protein described herein exhibits one, two, three, or four of improved duration of fusion protein expression, improved stability of the fusion protein on the cell surface, increased level of fusion protein expression, and/or decreased background activity of the fusion protein, e.g., relative to a macrophage without a fusion protein as described herein.

[0137] In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein decreases one or more signs and/or symptoms of an infection (e.g., of an infectious agent) in a subject, e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, an infectious agent comprises or is a virus, a protozoa (e.g., trypanosome, malaria, or toxoplasma), a bacteria (e.g., mycobacterium, salmonella, or listeria), a fungi (e.g., Candida), or a combination thereof. In some embodiments, a virus comprises hepatitis virus (e.g., hepatitis A, hepatitis B, hepatitis C, or hepatitis E), retrovirus, human immunodeficiency virus (e.g., HIV1 or HIV2), T cell leukemia virus, a

Lymphotropic virus (e.g., HTLV1 or HTLV2), herpes simplex virus (e.g., herpes simplex virus type 1 or type 2), Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, poliovirus, measles virus, Rubella virus, Japanese encephalitis virus, mumps virus, influenza virus, adenovirus, enterovirus, rhinovirus, coronavirus (e.g., severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)), Ebola virus, West Nile virus, or a variant or combination thereof.

[0138] In some embodiments, a macrophage comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein decreases formation and/or degrades existing aggregates via phagocytosis of at least one protein aggregate in a subject (e.g., a subject having a neurodegenerative disease, an inflammatory disease, a cardiovascular disease, a fibrotic disease, amyloidosis, or a combination thereof), e.g., relative to a macrophage without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a neurodegenerative disease is selected from the group consisting of tauopathy, a-synucleopathy, presenile dementia, senile dementia, Alzheimer's disease, progressive supranuclear palsy (PSP), Pick's disease, primary progressive aphasia, frontotemporal dementia, corticobasal dementia, Parkinson's disease, dementia with Lewy bodies, Down's syndrome, multiple system atrophy, amyotrophic lateral sclerosis (ALS), Hallervorden-Spatz syndrome, polyglutamine disease, trinucleotide repeat disease, and prion disease. In some embodiments, an inflammatory disease is selected from the group consisting of systemic lupus erythematosus, vasculitis, rheumatoid arthritis, periodontitis, ulcerative colitis, sinusitis, asthma, tuberculosis, Crohn’s disease, chronic infection, hereditary periodic fever, a malignancy, systemic vasculitides, cystic fibrosis, bronchiectasis, epidermolysis bullosa, cyclic neutropenia, an immunodeficiency, Muckle-Wells (MWS) disease, and Familiar Mediterranean Fever (FMF). In some embodiments, amyloidosis is selected from the group consisting of Primary Amyloidosis (AL), Secondary Amyloidosis (AA), Familial Amyloidosis (ATTR) , Beta-2 Microglobulin Amyloidosis, Localized Amyloidosis, Heavy Chain Amyloidosis (AH), Light Chain Amyloidosis (AL), Primary Systemic Amyloidosis, ApoAI Amyloidosis, ApoAII Amyloidosis, ApoAIV Amyloidosis, Apolipoprotein C2 Amyloidosis, Apolipoprotein C3 Amyloidosis, Corneal lactoferrin amyloidosis, Transthyretin-Related Amyloidosis, Dialysis amyloidosis, Fibrinogen amyloidosis, Lect2 amyloidosis (ALECT2), and Lysozyme amyloidosis. In some embodiments, a cardiovascular disease is selected from the group consisting of

atherosclerosis, coronary artery disease, peripheral artery disease, hypertensive heart disease, metabolic syndrome, hypertension, cerebrovascular disease, and heart failure. In some embodiments, a fibrotic disease is selected from the group consisting of pulmonary fibrosis, idiopathic pulmonary fibrosis, cirrhosis, cystic fibrosis, scleroderma, cardiac fibrosis, radiation-induced lung injury, steatohepatitis, glomerulosclerosis, interstitial lung disease, liver fibrosis, mediastinal fibrosis, retroperitoneal cavity fibrosis, bone marrow fibrosis, and skin fibrosis.

Monocytes

[0139] Monocytes are multipotent cells that circulate in the blood, bone marrow, and spleen, and generally do not proliferate when in a steady state. Monocytes can vary in size significantly in the range of about 10-30 μm in diameter. A ratio of nucleus to cytoplasm for a monocyte can range from about 2:1 to about 1:1. Typically, monocytes comprise chemokine receptors and pathogen recognition receptors that mediate migration from blood to tissues, such as during an infection. Monocytes can produce inflammatory cytokines, take up cells and/or toxic molecules, and differentiate into dendritic cells or macrophages.

[0140] In some embodiments, a monocyte comprises or expresses one or more phenotypic markers. Exemplarily phenotypic markers for human monocyte cells include, but are not limited to, CD9, CD11b, CD11c, CDw12, CD13, CD15, CDw17, CD31, CD32, CD33, CD35, CD36, CD38, CD43, CD49b, CD49e, CD49f, CD63, CD64, CD65s, CD68, CD84, CD85, CD86, CD87, CD89, CD91, CDw92, CD93, CD98, CD101, CD102, CD111, CD112, CD115, CD116, CD119, CDwl2lb, CDw123, CD127, CDw128, CDw131, CD147, CD155, CD156a, CD157, CD162 CD163, CD164, CD168, CD171, CD172a, CD180, CD206, CD131a1, CD213 2, CDw210, CD226, CD281, CD282, CD284, and CD286. Exemplarily phenotypic markers for mouse monocyte cells include, but are not limited to, CD11a, CD11b, CD16, CD18, CD29, CD31, CD32, CD44, CD45, CD49d, CD115, CD116, Cdw131, CD281, CD282, CD284, CD286, F4/80, and CD49b. In certain embodiments monocytes comprise one, two, or three of CD11b, CD14, or CD16. In certain embodiments, monocytes comprise CD14+ CD16- monocytes, CD14+ CD16+ monocytes, or CD14- CD16+ monocytes.

[0141] In some embodiments, a monocyte differentiates into a macrophage. In some embodiments, a monocyte differentiates into a dendritic cell (DC). Monocytes can be

differentiated into macrophages or DCs by any technique known in the art. For example, differentiation of monocytes into macrophages can be induced by macrophage colony stimulating factor (M-CSF). Differentiation of monocytes into DCs can be induced by granulocyte-macrophage colony stimulating factor (GM-CSF) in combination with IL-4.

[0142] In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased secretion of one or more cytokines (e.g., one, two, three, four, five, six, or seven of TNF, IL-12, IFN, GM-CSF, G-CSF, M-CSF, or IL-1), e.g., relative to a monocyte without an exogenous cytokine described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased phagocytosis, e.g., relative to a monocyte without an exogenous cytokine described as herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits enhanced survival, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits enhanced differentiation into macrophages (e.g., M1 or M2 macrophages), e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits enhanced differentiation into DCs (e.g., resident or migrating DCs and/or in lymphoid and non-lymphoid tissue), e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased cytotoxicity against a tumor cell, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased tumor antigen presentation (e.g., post-phagocytosis presentation) and/or increased antigen processing, e.g., relative to a monocyte without an exogenous cytokine as described

herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased tumor killing (e.g., by phagocytosis, lysis, apoptosis, or production of tumor killing cytokines (e.g., TNFα), e.g., relative to a monocyte without an exogenous cytokine described herein or a fusion protein as described herein.

[0143] In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one or both of increased expression of one or more genes typically associated with increased effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion) or decreased expression of one or more genes typically associated with decreased effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion), e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased production of ROS, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits metabolic reprogramming, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell survival mechanisms, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell death mechanisms, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one, two, three, four, or five of increased resistance to phagocytic checkpoints, increased expression of chemokine receptors to aid in trafficking, increased expression of chemokines to recruit other immune cells, increased expression of ECM degrading enzymes (e.g., MMPs to degrade tumor

ECM and/or exhibit anti fibrotic activity), or increased proliferation, e.g., relative to a monocyte without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a monocyte comprising or expressing at least one exogenous cytokine described herein and at least one CAR as described herein exhibits one, two, three, or four of improved duration of exogenous cytokine expression, improved stability of the CAR on the cell surface, increased level of exogenous cytokine expression, and/or decreased background activity of the exogenous cytokine, e.g., relative to a monocyte without an exogenous cytokine as described herein. In some embodiments, a monocyte comprising or expressing at least one fusion protein described herein exhibits one, two, three, or four of improved duration of fusion protein expression, improved stability of the fusion protein on the cell surface, increased level of fusion protein expression, or decreased background activity of the fusion protein, e.g., relative to a monocyte without a fusion protein as described herein.

Dendritic Cells

[0144] Dendritic cells (DCs) are bone marrow-derived, specialized antigen presenting cells that are involved in initiating immune responses and maintaining tolerance of the immune system to self-antigens. Dendritic cells may be found in both lymphoid and non-lymphoid organs and are generally thought to arise from lymphoid or myeloid lineages.

[0145] In some embodiments, a DC comprises or expresses one or more phenotypic markers. Exemplarily phenotypic markers for DCs include, but are not limited to, CD11c, CD83, CD1a, CD1c, CD141, CD207, CLEC9a, CD123, CD85, CD180, CD187, CD205, CD281, CD282, CD284, CD286 and partially CD206, CD207, CD208 and CD209.

[0146] Immature DCs can be characterized by a high capacity for antigen capture, but relatively low T cell stimulatory capability. Inflammatory mediators promote DC maturation. Once DCs reach the mature stage, there is a dramatic change in properties relative to immature DCs, such as a decrease in antigen capture ability and/or an increased ability to stimulate T cells. In some embodiments, a DC comprises or is an immature DC. In other embodiments, a DC comprises or is a mature DC.

[0147] Without wishing to be bound by theory, it is believed that modification of a DC cell to comprise or express at least one exogenous cytokine described herein or at least one fusion protein described herein can allow mature DCs to simultaneously exhibit increased antigen capture ability and T cell stimulation, e.g., relative to a DC without an exogenous cytokine described herein or a fusion protein described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein mediates tumor antigen presentation, e.g., increased tumor antigen presentation relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein mediates tumor T cell stimulation, e.g., increased T cell stimulation relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein.

[0148] In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased secretion of one or more cytokines (e.g., one, two, three, four, five, six, or seven of TNF, IL-12, IFN, GM-CSF, G-CSF, M-CSF, or IL-1), e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased phagocytosis, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits increased tumor antigen presentation (e.g., post-phagocytosis presentation), increased antigen processing, increased antigen cross presentation, increased T cell priming, and/or stimulation of T cells, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein.

[0149] In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one or both of increased expression of favorable genes or decreased expression of unfavorable genes, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous

cytokine described herein or at least one fusion protein described herein exhibits increased production of ROS, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits metabolic reprogramming, e.g., relative to a DC without an exogenous cytokine described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell survival mechanisms, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein.

[0150] In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits induction of cell death mechanisms, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein or at least one fusion protein described herein exhibits one, two, three, four, or five of increased resistance to phagocytic checkpoints, increased expression of chemokine receptors to aid in trafficking, increased expression of chemokines to recruit other immune cells, increased expression of ECM degrading enzymes (e.g., MMPs to degrade tumor ECM and/or exhibit anti fibrotic activity), or increased proliferation, e.g., relative to a DC without an exogenous cytokine as described herein or a fusion protein as described herein. In some embodiments, a DC comprising or expressing at least one exogenous cytokine described herein and at least one CAR as described herein exhibits one, two, three, or four of improved duration of exogenous cytokine expression, improved stability of the CAR on the cell surface, increased level of exogenous cytokine expression, and/or decreased background activity of the exogenous cytokine, e.g., relative to a DC without an exogenous cytokine as described herein. In some embodiments, a DC comprising or expressing at least one fusion protein described herein exhibits one, two, three, or four of improved duration of fusion protein expression, improved stability of the fusion protein on the cell surface, increased level of fusion protein expression, or decreased background activity of the fusion protein, e.g., relative to a DC without a fusion protein as described herein.

Methods of Immune Cell Modification

[0151] The present disclosure provides, among other things, methods for modifying an immune cell (e.g., a stem cell, monocyte, macrophage, or dendritic cell) comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR) into an immune cell. Methods can comprise delivering to an immune cell (e.g., a stem cell, monocyte, macrophage, or dendritic cell), a nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a CAR.

[0152] The present disclosure also provides, among other things, methods for modifying an immune cell (e.g., a stem cell, monocyte, macrophage, or dendritic cell) comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding a fusion protein or a fragment thereof into an immune cell. Methods can comprise delivering to an immune cell (e.g., a stem cell, monocyte, macrophage, or dendritic cell), a nucleic acid construct comprising one or more nucleic acids encoding: a fusion protein comprising a cytokine, a linker, and a cytokine receptor.

[0153] A nucleic acid construct comprising one or more nucleic acid sequences encoding at least one exogenous cytokine as described herein or at least one fusion protein as described herein can be introduced into an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) by physical, chemical, or biological methods. Physical methods for introducing a nucleic acid construct as described herein into an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) can comprise electroporation, calcium phosphate precipitation, lipofection, particle bombardment, microinjection, or a combination thereof. A nucleic acid construct can be introduced into immune cells using commercially available methods, including electroporation (Amaxa Nucleofector-II® (Amaxa Biosystems, Cologne, Germany), ECM 830 BTX (Harvard Instruments, Boston, Mass.) Gene Pulser II® (BioRad, Denver, Colo.), or Multiporator® (Eppendort, Hamburg Germany)). A nucleic acid construct can also be introduced into immune cells using mRNA transfection, e.g., cationic liposome-mediated transfection, lipofection, polymer encapsulation, peptide-mediated transfection, or biolistic particle delivery systems, such as “gene guns” (See, e.g., Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001), which is hereby incorporated by reference in its entirety).

[0154] Biological methods for introducing a nucleic acid construct as described herein into an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) include use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become widely used for inserting genes into mammalian cells (e.g., human cells). Viral vectors can also be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses (e.g. Ad5f35), or adeno-associated viruses (See, e.g., U.S. Patent Nos. 5,350,674 and 5,585,362, which are hereby incorporated by reference in their entirety). Retroviral vectors, such as lentivirus, are suitable tools to achieve long-term gene transfer that allow for long-term, stable integration of a transgene and its propagation in daughter cells. In some embodiments, a lentiviral vector is packaged with a Vpx protein (e.g., as described in International Publication No. WO 2017/044487, which is hereby incorporated by reference in its entirety). In some embodiments, Vpx comprises a virion-associated protein (e.g., an accessory protein for viral replication). In some embodiments, a Vpx protein is encoded by human immunodeficiency virus type 2 (HIV-2). In some embodiments, a Vpx protein is encoded by simian immunodeficiency virus (SIV). In some embodiments, an immune cell as described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell) is transfected with a lentiviral vector packaged with a Vpx protein. In some embodiments, Vpx inhibits at least one antiviral factor of an immune cell as described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell). In some embodiments, a lentiviral vector packaged with a Vpx protein exhibits increased transfection efficiency of an immune cell as described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell), e.g., relative to a lentiviral vector not packaged with a Vpx protein. In some embodiments, an immune cell as described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell) is one or both of electroporated or transfected with at least one VPX mRNA prior to transfection with a viral vector (e.g., an adenoviral vector, e.g., an Ad2 vector or an Ad5 vector (e.g., Ad5f35 adenoviral vector, e.g., a helper-dependent Ad5F35 adenoviral vector)).

[0155] Chemical means for introducing a nucleic acid construct as described herein into an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) include colloidal dispersion systems, macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems (e.g., oil-in-water emulsions, micelles, mixed micelles, nanoparticles, liposomes, and lipofectamine-nucleic acid complexes).

[0156] An exemplary system for delivery of a nucleic acid construct as described herein is a lipid-based system. A nucleic acid construct as described herein may be encapsulated in an aqueous interior of a liposome, interspersed within a lipid bilayer, attached to a liposome via a linking molecule, entrapped in a liposome, complexed with a liposome, dispersed in a solution or suspension comprising a lipid, mixed with a lipid, complexed with a micelle, or otherwise associated with a lipid. Lipids for use in methods described herein may be naturally occurring or synthetic lipids. Lipids can also be obtained from commercial sources. For example, dimyristyl phosphatidylcholine can be obtained from Sigma (St. Louis, MO); dicetyl phosphate can be obtained from K & K Laboratories (Plainview, NY); cholesterol can be obtained from Calbiochem-Behring; and dimyristyl phosphatidylglycerol can be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20℃.

[0157] In some embodiments of the present disclosure, a nucleic acid construct is or comprises an mRNA. In some embodiments, mRNA according to the present disclosure may be synthesized as unmodified or modified mRNA. Typically, mRNAs are modified to enhance stability. Modifications of mRNA can include, for example, modifications of the nucleotides of the RNA. A modified mRNA according to the present disclosure can thus include, for example, backbone modifications, sugar modifications or base modifications. In some embodiments, a step of modifying an mRNA comprises causing the mRNA to include a modified nucleotide, an alteration to the 5' or 3' untranslated region (UTR), a cap structure, and/or a poly(A) tail.

[0158] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) may contain RNA backbone modifications. Typically, a backbone modification is a modification in which the phosphates of the backbone of the nucleotides contained in the RNA are modified chemically. Exemplary backbone modifications typically include, but are not limited to, modifications from the group consisting of methylphosphonates, methylphosphoramidates, phosphoramidates, phosphorothioates (e.g. cytidine 5'-O-(1-thiophosphate)), boranophosphates, positively charged guanidinium groups etc., which comprises replacing the phosphodiester linkage by other anionic, cationic or neutral groups.

[0159] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) may contain sugar modifications. A typical sugar modification is a chemical modification of the sugar of the nucleotides it contains including, but not limited to, sugar modifications chosen from the group consisting of 2'-deoxy-2'-fluoro-oligoribonucleotide (2'-fluoro-2'-deoxycytidine 5'-triphosphate, 2'-fluoro-2'-deoxyuridine 5'-triphosphate), 2'-deoxy-2'-deamine-oligoribonucleotide (2'-amino-2'-deoxycytidine 5'-triphosphate, 2'-amino-2'-deoxyuridine 5'-triphosphate), 2'-O-alkyloligoribonucleotide, 2'-deoxy-2'-C-alkyloligoribonucleotide (2'-O-methylcytidine 5'-triphosphate, 2'-methyluridine 5'-triphosphate), 2'-C-alkyloligoribonucleotide, and isomers thereof (2'-aracytidine 5'-triphosphate, 2'-arauridine 5'-triphosphate), or azidotriphosphates (2'-azido-2'-deoxycytidine 5'-triphosphate, 2'-azido-2'-deoxyuridine 5'-triphosphate).

[0160] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) may contain modifications of the bases of the nucleotides (base modifications). A modified nucleotide which contains a base modification is also called a base-modified nucleotide.

[0161] Typically, mRNA synthesis includes the addition of a “cap” on the N-terminal (5’) end, and a “tail” on the C-terminal (3’) end. The presence of the cap is important in providing resistance to nucleases found in most eukaryotic cells. The presence of a “tail” serves to protect the mRNA from exonuclease degradation.

[0162] Thus, in some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) include a 5’ cap structure. A 5’ cap is typically added as follows: first, an RNA terminal phosphatase removes one of the terminal phosphate groups from the 5’ nucleotide, leaving two terminal phosphates; guanosine triphosphate (GTP) is then added to the terminal phosphates via a guanylyl transferase, producing a 5’ triphosphate linkage; and the 7-nitrogen of guanine is then methylated by a methyltransferase. Examples of cap structures include, but are not limited to, m7G(5')ppp (5'(A,G(5')ppp(5')A and G(5')ppp(5')G. In some embodiments, a cap comprises a Cap0 structure. A cap0 structures lack a 2'-O-methyl residue of the ribose attached to bases 1 and 2. In some embodiments, a cap comprises an AGCap1 structure. An AGCap1 structures has a 2'-O-methyl residue at base 2. In some embodiments, a cap comprises a Cap2 structure. Cap2

structures have a 2'-O-methyl residue attached to both bases 2 and 3. In some embodiments, a cap structure comprises AGCap1, m6AGCap1, or Anti-Reverse Cap Analog (ARCA). In some embodiments, a modified mRNA of the present disclosure comprises an m6AGCap1 and modified nucleotides comprising pseudouridine (PsU).

[0163] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) include a 3' poly(A) tail structure. A poly(A) tail on the 3' terminus of mRNA typically includes about 10 to 400 adenosine nucleotides (SEQ ID NO: 176) (e.g., about 100 to 400 adenosine nucleotides, about 10 to 200 adenosine nucleotides, about 10 to 150 adenosine nucleotides, about 10 to 100 adenosine nucleotides, about 20 to 70 adenosine nucleotides, or about 20 to 60 adenosine nucleotides). In some embodiments, mRNAs include a 3' poly(C) tail structure. A suitable poly(C) tail on the 3' terminus of mRNA typically include about 10 to 200 cytosine nucleotides (SEQ ID NO: 177) (e.g., about 10 to 150 cytosine nucleotides, about 10 to 100 cytosine nucleotides, about 20 to 70 cytosine nucleotides, about 20 to 60 cytosine nucleotides, or about 10 to 40 cytosine nucleotides). A poly(C) tail may be added to a poly(A) tail or may be a substitute for the poly(A) tail.

[0164] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding exogenous cytokines, mRNAs encoding CARs, or mRNAs encoding fusion proteins) include a 5' and/or 3' untranslated region. In some embodiments, a 5' untranslated region includes one or more elements that affect an mRNA's stability or translation, for example, an iron responsive element. In some embodiments, a 5' untranslated region may be between about 50 and 500 nucleotides in length.

[0165] In some embodiments, a 3' untranslated region includes one or more of a polyadenylation signal, a binding site for proteins that affect an mRNA's stability of location in a cell, or one or more binding sites for miRNAs. In some embodiments, a 3' untranslated region may be between 50 and 500 nucleotides in length or longer.

Treatment and Culturing of Immune Cells During Modification

[0166] In some embodiments, methods of the present disclosure comprise one or more steps of treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) during the process of modifying the immune cell.

[0167] In some embodiments, methods of the present disclosure comprise a step of treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a modulator of a pathway activated by in vitro transcribed mRNA. In vitro transcribed (IVT) mRNA is recognized by various endosomal innate immune receptors (Toll-like receptor 3 (TLR3), TLR7 and TLR8) and cytoplasmic innate immune receptors (protein kinase RNA-activated (PKR), retinoic acid-inducible gene I protein (RIG-I), melanoma differentiation-associated protein 5 (MDA5) and 2′-5′-oligoadenylate synthase (OAS)). Signaling through these different pathways results in inflammation associated with type 1 interferon (IFN), tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-12 and the activation of cascades of transcriptional programs. Overall, these create a pro-inflammatory microenvironment poised for inducing specific immune responses. Moreover, downstream effects such as slow-down of translation by eukaryotic translation initiation factor 2α (eIF2α) phosphorylation, enhanced RNA degradation by ribonuclease L (RNaseL), and overexpression and inhibition of replication of self-amplifying mRNA are of relevance for the pharmacokinetics and pharmacodynamics of IVT mRNA.

[0168] In some embodiments, a modulator of a pathway activated by in vitro transcribed mRNA comprises an RNase inhibitor. In some embodiments, a modulator of a pathway activated by in vitro transcribed mRNA comprises an RNaseL, RNase T2 or RNase1 inhibitor. In some embodiments, a modulator of a pathway activated by in vitro transcribed mRNA comprises an RNaseL inhibitor. In some embodiments, an RNaseL inhibitor comprises sunitinib. In some embodiments, an RNaseL inhibitor comprises ABCE1.

[0169] In some embodiments, treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with an RNaseL inhibitor increases mRNA stability in a modified immune cell relative to mRNA stability in a modified immune cell of the same type that was not treated with an RNaseL inhibitor. In some embodiments, treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with an RNaseL inhibitor increases exogenous

cytokine expression in a modified immune cell relative to exogenous cytokine expression in a modified immune cell of the same type that was not treated with an RNaseL inhibitor. In some embodiments, treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with an RNaseL inhibitor increases fusion protein expression in a modified immune cell relative to fusion protein expression in a modified immune cell of the same type that was not treated with an RNaseL inhibitor. In some embodiments, treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with an RNaseL inhibitor increases effector activity in a modified immune cell relative to effector activity in a modified immune cell of the same type that was not treated with an RNaseL inhibitor.

[0170] In some embodiments of the present disclosure, a step of treating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) occurs before a step of delivering an mRNA to the immune cell.

[0171] In some embodiments, methods of the present disclosure comprise a step of culturing an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein. In some embodiments, a cytokine comprises IFN-α, IFN-β, IFN-γ, TNFα, IL-6, STNGL, LPS, a CD40 agonist, a 4-1BB ligand, recombinant 4-1BB, a CD19 agonist, a TLR agonist (e.g., TLR-1, TLR-2, TLR-3, TLR-4, TLR-5, TLR-6, TLR-7, TLR-8 or TLR-9), TGF-β (e.g., TGF-β1, TGF- β2, or TGF-β3), a glucocorticoid, an immune complex, interleukin-1 alpha (IL-1α), IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-20, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), Leukemia inhibitory factor (LIF), oncostatin M (OSM), TNF-β, CD154, lymphotoxin beta (LT-β), an A proliferation-inducing ligand (APRIL), CD70, CD153, glucocorticoid-induced TNF receptor ligand (GITRL), tumor necrosis factor superfamily member 14 (TNFSF14), OX40L (CD252), TALL-1 (Tumor necrosis factor ligand superfamily member 13B - TNFSF13B), TNF-related apoptosis-inducing ligand (TRAIL), TNF-related weak inducer of apoptosis (TWEAK), TNF-related activation-induced cytokine (TRANCE), erythropoietin (Epo), thyroid peroxidase precursor (Tpo), FMS-related tyrosine kinase 3 ligand (FLT-3L), stem cell factor (SCF), macrophage colony-stimulating factor (M-CSF), merozoite surface protein (MSP), a Nucleotide-binding oligomerization domain-containing protein (NOD) ligand (e.g., NOD1, NOD2, or

NOD1/2 agonists), a RIG-I-like receptor (RLR) ligand (e.g., 5'ppp-dsRNA, 3p-hpRNA, Poly(I:C), or Poly(dA:dT)), a C-type lectin receptor (CLR) ligand (e.g., curdlan, β-glucan, HKCA, laminarin, pustulan, scleroglucan, WGP dispersible, WGP soluble, zymosan, zymosan depleted, furfurman, b-GlcCer, GlcC14C18, HKMT, TDB, TDB-HS15, or TDM), a cyclic dinucleotide sensor ligand (e.g., C-Gas agonist or stimulator of interferon gene (STING) ligand), an inflammasome inducer (e.g., alum, ATP, CPPD crystals, hemozoin, MSU crystals, Nano-SiO2, Nigericin, or TDB), an aryl hydrocarbon (AhR) ligand (e.g., FICZ, indirubin, ITE, or L-kynurenine), an alpha-protein kinase 1 (ALPK1) ligand, a multi-PRR ligand, an NFKB/NFAT activator (e.g., concavalin A, ionomycin, PHA-P, or PMA) or a combination thereof. In some embodiments, a cytokine comprises IFN-β.

[0172] In some embodiments of the present disclosure, a step of culturing an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) occurs after a step of delivering an mRNA to the immune cell.

[0173] In some embodiments, culturing a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein increases the viability of the modified immune cell relative to a modified immune cell of the same type that was not cultured with the cytokine or immune stimulating recombinant protein. In some embodiments, culturing a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein increases protein (e.g., exogenous cytokine, CAR, or fusion protein) expression of the modified immune cell relative to a modified immune cell of the same type that was not cultured with the cytokine or immune stimulating recombinant protein. In some embodiments, culturing a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein increases longevity of protein (e.g., exogenous cytokine, CAR, or fusion protein) expression relative to a modified immune cell of the same type that was not cultured with the cytokine or immune stimulating recombinant protein. In some embodiments, culturing a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein increases effector activity of the modified immune cell relative to a modified immune cell of the same type that was not cultured with the cytokine or immune stimulating recombinant protein.

In some embodiments, culturing a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) with a cytokine or immune stimulating recombinant protein increases pro-inflammatory (M1) polarization of the modified immune cell relative to a modified immune cell of the same type that was not cultured with the cytokine or immune stimulating recombinant protein.

Modified Immune Cells

[0174] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) is made by methods of the present disclosure. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased viability relative to a modified immune cell of the same type comprising unmodified mRNA encoding an exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased expression of an mRNA encoding an exogenous cytokine and/or CAR relative to a modified immune cell of the same type comprising unmodified mRNA encoding the exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased exogenous cytokine and/or CAR expression relative to a modified immune cell of the same type comprising unmodified mRNA encoding the exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased longevity of an mRNA encoding an exogenous cytokine and/or CAR relative to a modified immune cell of the same type comprising unmodified mRNA encoding the exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased longevity of an exogenous cytokine and/or CAR relative to a modified immune cell of the same type comprising unmodified mRNA

encoding the exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased effector activity relative to a modified immune cell of the same type comprising unmodified mRNA encoding an exogenous cytokine and/or CAR. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding an exogenous cytokine and/or CAR as provided herein exhibits increased pro-inflammatory (M1) polarization relative to a modified immune cell of the same type comprising unmodified mRNA encoding an exogenous cytokine and/or CAR.

[0175] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) is made by methods of the present disclosure. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased viability relative to a modified immune cell of the same type comprising unmodified mRNA encoding a fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased expression of an mRNA encoding a fusion protein relative to a modified immune cell of the same type comprising unmodified mRNA encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased fusion protein expression relative to a modified immune cell of the same type comprising unmodified mRNA encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased longevity of an mRNA encoding a fusion protein relative to a modified immune cell of the same type comprising unmodified mRNA encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased longevity of a fusion protein relative to a modified immune cell of the same type comprising unmodified mRNA encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided

herein exhibits increased effector activity relative to a modified immune cell of the same type comprising unmodified mRNA encoding a fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a modified mRNA encoding a fusion protein as provided herein exhibits increased pro-inflammatory (M1) polarization relative to a modified immune cell of the same type comprising unmodified mRNA encoding a fusion protein.

Assays

[0176] A variety of assays may be performed to confirm the presence of a nucleic acid construct as described herein in an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell). For example, such assays include molecular biological assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR, and PCR; and biochemical assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots). Other assays of the present disclosure, include, for example, fluorescence-activated cell sorting (FACS), immunofluorescent microscopy, MSD cytokine analysis, mass spectrometry (MS), RNA-Seq and functional assays.

[0177] A variety of assays may be performed to determine various characteristics of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell), such as, but not limited to, immune cell viability, nucleic acid expression, nucleic acid longevity, protein (e.g., exogenous cytokine, CAR, or fusion protein) expression, protein (e.g., exogenous cytokine, CAR, or fusion protein) longevity, effector activity, and pro-inflammatory (M1) polarization. For example, such assays include flow cytometry, quantitative PCR, and in vitro functional assays such as cytokine/chemokine secretion, phagocytosis, and specific lysis assays of target tumor cells.

Exogenous Cytokines

[0178] In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) of the present disclosure do not comprise fusion proteins. In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) of the

present disclosure comprise at least one exogenous cytokine and at least one chimeric antigen receptor (CAR). As used herein, the term "exogenous cytokine" refers to a cytokine produced as a result of the introduction of an exogenous nucleic acid material (e.g., DNA or RNA) encoding the cytokine into an immune cell. In some embodiments, an exogenous cytokine is or comprises a pro-inflammatory (M1) cytokine. In some embodiments, a pro-inflammatory cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, or GM-CSF. In some embodiments, an exogenous cytokine is or comprises an anti-inflammatory (M2) cytokine. In some embodiments, an anti-inflammatory cytokine is or comprises IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β. In some embodiments, a cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β. In some embodiments, a cytokine is selected from **Table 1**.

[0179] In some embodiments, an exogenous cytokine of the present invention comprises the same linear amino acid sequence as an endogenous cytokine (e.g., sequences in **Table 2a** and **Table 2b**). In some embodiments, an exogenous cytokine of the present invention comprises a cytokine comprising an engineered amino acid sequence (e.g., sequences in **Table 6**). In some embodiments, an engineered cytokine amino acid sequence is derived from an endogenous cytokine sequence.

[0180] In some embodiments, an exogenous cytokine is or comprises a circular permutation. A circular permutation is a version of a protein wherein sections of amino acids are rearranged such that a region of amino acids in the middle of an endogenous protein is instead at the N-terminal or C-terminal end, but with the resulting protein still having an overall three-dimensional shape similar to the endogenous protein. In some embodiments, an exogenous cytokine comprising a circular permutation of the cytokine will have increased binding between the cytokine and its corresponding cytokine receptor relative to an exogenous cytokine comprising the same linear amino acid sequence as an endogenous cytokine. In some

embodiments, an exogenous cytokine comprising a circular permutation of the cytokine will have increased signaling relative to an exogenous cytokine comprising the same linear amino acid sequence as an endogenous cytokine. In some embodiments, an exogenous cytokine of the present invention comprises a circular permutation of IL-1β, IL-4, IL-10, or IL-13.

[0181] In some embodiments, an exogenous cytokine is or comprises a single-chain cytokine. As used herein, a single-chain cytokine comprises two or more copies of a cytokine fused together. In some embodiments, the two or more copies of a cytokine in a single-chain cytokine are separated by a linker. In some embodiments, a single-chain cytokine allows an exogenous cytokine of the present disclosure to mimic an endogenous cytokine that acts as a multimer when binding to its corresponding cytokine receptor. In some embodiments, an exogenous cytokine of the present invention comprises a single-chain cytokine comprising two or more copies of IFN-γ, TNF-α, IL-12, or IL-10.

[0182] In some embodiments, an exogenous cytokine is or comprises a monomeric cytokine. As used herein, a monomeric cytokine has been engineered so that it does not need to multimerize (e.g., dimerize or trimerize) in order to bind to its corresponding cytokine receptor. In some embodiments, an exogenous cytokine of the present invention comprises a monomeric cytokine comprising an engineered version of IFN-γ, TNF-α, IL-12, or IL-10.

[0183] In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 80% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 85% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 90% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 95% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 96% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 97% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises

an amino acid sequence at least 98% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence at least 99% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, an exogenous cytokine of the present disclosure comprises an amino acid sequence identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**.

[0184] In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, an exogenous cytokine of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**.

Fusion Proteins

[0185] The term “fusion protein”, as used herein, refers to an artificial chimeric protein comprising a cytokine fused to at least one of its corresponding receptor subunits, such that the

cytokine can intramolecularly bind its tethered receptor and induce downstream signaling. Fusion proteins may be used, for example, as a therapy with adoptive cell transfer. For example, in some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells are removed from a patient (e.g., from blood, tumor or ascites fluid) and modified so that they express a fusion protein. In some embodiments, such modified immune cells are then reintroduced to the same or a different patient as a therapeutic.

[0186] In some embodiments, a fusion protein may comprise one or more of: one or more cytokines, one or more linkers and one or more cytokine receptors (see **Figure 1**). In some embodiments, fusion proteins of the present disclosure are membrane-bound. In some embodiments, fusion proteins of the present disclosure are not membrane-bound.

[0187] In embodiments, a fusion protein of the present disclosure further comprises a signal peptide. In some embodiments, a fusion protein comprises, from N-terminus to C-terminus: a signal peptide, a cytokine, a linker, and a cytokine receptor (see Figure 2).

[0188] In some embodiments, a fusion protein comprises a linker between cytokine and a cytokine receptor. As used herein, the term "linker" refers to any oligo- or polypeptide that functions to link a cytokine to a cytokine receptor in a polypeptide chain in a fusion protein of the present disclosure. In some embodiments, a linker may comprise up to 300 amino acids, preferably 5 to 100 amino acids and most preferably 5 to 30 amino acids.

[0189] In some embodiments, an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein may comprise one or more control systems including, but not limited to: a safety switch (e.g., an on switch, an off switch, a suicide switch), transcriptional control (e.g. cell-specific promoters, cell-state specific promoters, promoters downstream of fusion protein activation, promoters downstream of endogenous signaling pathways, or drug-inducible transcription), post-transcriptional control of fusion protein mRNA (e.g. RNA-based inhibition with endogenous or recombinant miRNA), or post-translational control of a fusion protein's structure or stability (e.g. a fusion protein whose intracellular domain conditionally associates with the full structure by drug/light-inducible association (to allow signaling) or dissociation (to inhibit signaling), or whose stability is drug-regulated for inducible stabilization (to allow signaling) or degradation (to inhibit signaling)). These control systems can be combined to create logic gates, for example an AND gate (e.g. a fusion protein

with a fusion protein-inducible promoter and cytosolic domain that associates in a drug-dependent manner, thus requiring fusion protein activation and the presence of a small molecule), an OR gate (e.g. a fusion protein under control of a promoter that is transcriptionally active following either fusion protein activation or small molecule addition), and/or a NOT gate (e.g. a fusion protein whose mRNA is degraded by endogenous miRNA's expressed in natural immune cell signaling states (such as miRNA's upregulated by a particular cytokine signaling pathway, thus only expressing fusion protein in the absence of this cytokine)).In some embodiments, a modified immune cell, for example, a modified stem cell, macrophage, monocyte, or dendritic cell, is generated by expressing a fusion protein therein. In some embodiments, an immune cell comprises a fusion protein comprising a cytokine, a linker, and a cytokine receptor, wherein the immune cell comprises a stem cell, macrophage, monocyte, or dendritic cell, and wherein the cytokine binds the cytokine receptor.

[0190] In some embodiments, a fusion protein of the present disclosure comprises a cytokine selected from **Table 1** and the corresponding Receptor 1 selected from the same row in **Table 1**. In some embodiments, a fusion protein of the present disclosure comprises a cytokine selected from **Table 1** and the corresponding Receptor 2/Co-Receptor selected from the same row in **Table 1**.

Table 1 - Cytokines and Corresponding Receptors

Cytokine	M1/M2	Receptor 1	Receptor 2 or Co-Receptor
IFN-α2	M1	IFNAR1	IFNAR2
IFN-β	M1	IFNAR1	IFNAR2
IFN-γ	M1	IFNGR1	IFNGR2
TNF-α	M1	TNFR1	TNFR2
IL-1β	M1	IL-1R1	IL-1R3
IL-6	M1	IL-6Rα	gp130
IL-12	M1	IL-12-Rβ1	IL-12-Rβ2
IL-4	M2	IL-4Rα	IL-2Rγc or IL-13Rα1
IL-10	M2	IL-10R1	IL-10R2
IL-13	M2	IL-13Rα1	IL-4Rα
IL-18	M2	IL-18Rα	IL-18Rβ

[0191] In some embodiments, a fusion protein of the present disclosure comprises interleukin 10 (IL-10), a linker, and interleukin-10 receptor (IL10R).

[0192] In some embodiments, a fusion protein of the present disclosure comprises interferon beta (IFNβ), a linker, and interferon-α/β receptor (IFNAR).

[0193] In some embodiments, a modified immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) further comprises a chimeric antigen receptor (CAR) of the present disclosure.

[0194] The present disclosure also provides immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) comprising a nucleic acid sequence (e.g., an isolated nucleic acid sequence) encoding a fusion protein, wherein the nucleic acid sequence comprises a nucleic acid sequence encoding a cytokine, a nucleic acid sequence encoding a linker and a nucleic acid sequence encoding a cytokine receptor, wherein the cell is a stem cell, macrophage, monocyte or dendritic cell that expresses the fusion protein.

[0195] In some embodiments, a fusion protein comprises a cytokine that is operably linked to another domain of the fusion protein, such as a cytokine receptor, for expression in an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell).

[0196] In some embodiments, a fusion protein of the present disclosure is expressed at the surface of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell). In some embodiments, a fusion protein of the present disclosure induces a pro-inflammatory phenotype, as indicated by cytokine production, gene expression changes, cell surface markers, and/or functional assays. In some embodiments, a fusion protein of the present disclosure induces an anti-inflammatory phenotype, as indicated by cytokine production, gene expression changes, cell surface markers, and/or functional assays.

[0197] In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 80% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 85% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 90% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure

comprises an amino acid sequence at least 95% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 96% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 97% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 98% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 99% identical to a sequence selected from Table 9. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence identical to a sequence selected from Table 9.

[0198] In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a sequence selected from Table 10. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a sequence selected from Table 10.

[0199] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains a

pro-inflammatory phenotype over time. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains a pro-inflammatory phenotype at least 4 hours, 2 days, 4 days, 7 days, 14 days, and/or 28 days after an immune cell is modified with a nucleic acid encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains a pro-inflammatory phenotype longer than an immune cell induced by pre-treatment with a soluble cytokine.

[0200] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains an anti-inflammatory phenotype over time. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains an anti-inflammatory phenotype at least 4 hours, 2 days, 4 days, 7 days, 14 days, and/or 28 days after an immune cell is modified with a nucleic acid encoding the fusion protein. In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains an anti-inflammatory phenotype longer than an immune cell induced by pre-treatment with a soluble cytokine.

[0201] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains a pro-inflammatory phenotype and/or otherwise resists subversion when challenged by anti-inflammatory cytokines. In some embodiments, the sensitivity of a modified immune cell to environmental cytokines is measured by generating a dose-response curve of pro-inflammatory markers by treating modified immune cells comprising pro-inflammatory fusion proteins with increasing concentrations of anti-inflammatory cytokines. In some embodiments, the sensitivity of a modified immune cell to environmental cytokines is measured by generating a dose-response curve of pro-inflammatory markers by treating modified immune cells comprising pro-inflammatory fusion proteins with increasing concentrations of pro-inflammatory cytokines (e.g., quantifying the effect of soluble IFN-β on modified immune cells comprising an IFN-β fusion protein).

[0202] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure maintains an anti-inflammatory phenotype and/or otherwise resists subversion when challenged by pro-inflammatory cytokines. In some embodiments, the sensitivity of a modified immune cell to environmental cytokines is measured by generating a dose-response curve of anti-inflammatory markers by treating modified immune cells comprising anti-inflammatory fusion proteins with increasing concentrations of pro-inflammatory cytokines. In some embodiments, the sensitivity of a modified immune cell to environmental cytokines is measured by generating a dose-response curve of anti-inflammatory markers by treating modified immune cells comprising anti-inflammatory fusion proteins with increasing concentrations of anti-inflammatory cytokines (e.g., quantifying the effect of soluble IL-10 on modified immune cells comprising an IL-10 fusion protein).

[0203] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure has minimal effects on neighboring cells. In some embodiments, the effect of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure on an unmodified cell (e.g., an immune cell that doesn't comprise a fusion protein of the present disclosure) can be tested by co-culturing modified immune cells with unmodified immune cells and using flow cytometry to analyze the expression of pro-inflammatory and anti-inflammatory markers in the unmodified cells. In some embodiments, modified immune cells and unmodified immune cells can be co-cultured in a culture dish where the modified immune cells and unmodified immune cells contact each other. In some embodiments, modified immune cells and unmodified immune cells can be co-cultured in a culture dish where the modified immune cells and unmodified immune cells are separated by a transwell assay membrane. In some embodiments, a positive control for testing the effect of modified immune cells on unmodified immune cells comprises modified immune cells that express soluble cytokine that can diffuse to stimulate neighboring cells, instead of a fusion protein of the present disclosure.

[0204] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a fusion protein of the present disclosure has minimal cytotoxic effects on neighboring cells. In some embodiments, modifying an immune cell to

comprise a fusion protein of the present disclosure is not cytotoxic to the modified immune cell. In some embodiments, RNAseq data from modified immune cells are examined to determine if upregulation of genes indicative of cytotoxic effects is present.

[0205] In some embodiments, expression of a fusion protein of the present disclosure in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) also comprising a CAR does not decrease a targeted effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion) of the modified immune cell relative to a modified immune cell comprising the CAR but not comprising the fusion protein. In some embodiments, expression of a fusion protein of the present disclosure in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) also comprising a CAR increases a targeted effector function (e.g., phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion) of the modified immune cell relative to a modified immune cell comprising the CAR but not comprising the fusion protein.

Cytokines

[0206] The present disclosure provides fusion proteins comprising cytokines. In some embodiments, a cytokine is or comprises a pro-inflammatory (M1) cytokine. In some embodiments, a pro-inflammatory cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, or GM-CSF. In some embodiments, a cytokine is or comprises an anti-inflammatory (M2) cytokine. In some embodiments, an anti-inflammatory cytokine is or comprises IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β. In some embodiments, a cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β . In some embodiments, a cytokine is selected from **Table 1**.

[0207] In some embodiments, a fusion protein of the present invention comprises a cytokine comprising the same linear amino acid sequence as an endogenous cytokine (e.g., sequences in **Table 2a** and **Table 2b**). In some embodiments, a fusion protein of the present invention comprises a cytokine comprising an engineered amino acid sequence (e.g., sequences in **Table 6**). In some embodiments, an engineered cytokine amino acid sequence is derived from an endogenous cytokine sequence.

[0208] In some embodiments, an engineered cytokine is or comprises a circular permutation. A circular permutation is a version of a protein wherein sections of amino acids are rearranged such that a region of amino acids in the middle of an endogenous protein is instead at the N-terminal or C-terminal end, but with the resulting protein still having an overall three-dimensional shape similar to the endogenous protein. In some embodiments, a fusion protein comprising a circular permutation of a cytokine will have increased binding between the cytokine and the cytokine receptor relative to a fusion protein comprising a cytokine comprising the same linear amino acid sequence as an endogenous cytokine. In some embodiments, a fusion protein comprising a circular permutation of a cytokine will have increased signaling relative to a fusion protein comprising a cytokine comprising the same linear amino acid sequence as an endogenous cytokine. In some embodiments, a fusion protein comprising a circular permutation of a cytokine comprises a shorter linker relative to a fusion protein comprising a cytokine comprising the same linear amino acid sequence as an endogenous cytokine. In some embodiments, a fusion protein of the present invention comprises a circular permutation of IL-1β, IL-4, IL-10, or IL-13.

[0209] In some embodiments, an engineered cytokine is or comprises a single-chain cytokine. As used herein, a single-chain cytokine comprises two or more copies of a cytokine fused together. In some embodiments, the two or more copies of a cytokine in a single-chain cytokine are separated by a linker. In some embodiments, a single-chain cytokine allows a fusion protein of the present disclosure to mimic an endogenous cytokine that acts as a multimer when binding to the cytokine receptor. In some embodiments, a fusion protein of the present invention comprises a single-chain cytokine comprising two or more copies of IFN-γ, TNF-α, IL-12, or IL-10.

[0210] In some embodiments, an engineered cytokine is or comprises a monomeric cytokine. As used herein, a monomeric cytokine has been engineered so that it does not need to multimerize (e.g., dimerize or trimerize) in order to bind to its corresponding cytokine receptor. In some embodiments, a fusion protein of the present invention comprises a monomeric cytokine comprising an engineered version of IFN-γ, TNF-α, IL-12, or IL-10.

[0211] In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 80% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 85% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 90% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 95% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 96% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 97% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 98% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 99% identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence identical to a sequence selected from **Table 2a**, **Table 2b**, or **Table 6**.

[0212] In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some

embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a sequence selected from **Table 4a**, **Table 4b**, or **Table 7**.

Linkers

[0213] In some embodiments, a fusion protein of the present disclosure comprises a linker. In some embodiments, a fusion protein of the present disclosure comprises a linker between the cytokine and cytokine receptor. In some embodiments, the linker is a flexible linker. In some embodiments, a flexible linker comprises predominantly small amino acids, either non-polar (e.g., serine or threonine) or polar (e.g., glycine). In some embodiments, a flexible linker comprises amino acid substitutions (e.g., lysine, glutamic acid, glutamine, aspartic acid, and/or asparagine) relative to a known linker in order to improve solubility of the linker. In some embodiments, the flexibility of a linker is determined using circular dichroism spectroscopy to test if a linker is folded into a helix (i.e., a rigid structure) or a non-structured (i.e., flexible) coil. In some embodiments, the linker is a cleavable linker. In some embodiments, a linker comprises 5-50 amino acids. In some embodiments, a linker comprises 19-26 amino acids. In some embodiments, a linker comprises 26 amino acids. In some embodiments, a linker is at least 90 angstroms in length. In some embodiments, a linker

comprises amino acids selected from glycine (G), serine (S), threonine (T), lysine (K), proline (P), glutamic acid (E), glutamine (Q), aspartic acid (D), asparagine (N), or alanine (A).

[0214] In some embodiments, a linker is or comprises a linker selected from a group consisting of: a $(G4S)_n$ linker (wherein n = 1-5) **(SEQ ID NO: 170)**, a Whitlow linker, and Linker 26.

[0215] In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 80% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 85% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 90% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 95% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 96% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 97% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 98% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 99% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence identical to a linker sequence selected from **Table 8**.

[0216] In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 80% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of

the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a linker sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a linker sequence selected from **Table 8**.

Cytokine Receptors

[0217] The present disclosure provides fusion proteins comprising cytokine receptors. In some embodiments, a cytokine receptor is or comprises a pro-inflammatory (M1) cytokine receptor. In some embodiments, a pro-inflammatory cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, or CSF2-Rβ. In some embodiments, a cytokine receptor is or comprises an anti-inflammatory (M2) cytokine receptor. In some embodiments, an anti-inflammatory cytokine receptor is or comprises IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2. In some embodiments, a cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2.

[0218] In some embodiments, a fusion protein of the present invention comprises a cytokine receptor comprising the same linear amino acid sequence as an endogenous cytokine (e.g., sequences in **Table 3a** and **Table 3b**). In some embodiments, a fusion protein of the present invention comprises a cytokine receptor comprising an engineered amino acid sequence. In some embodiments, an engineered cytokine amino acid sequence is derived from an endogenous cytokine sequence.

[0219] Many cytokines, including IFN-β and IL-10, signal through heterodimeric receptor complexes. In some embodiments, a fusion protein of the present disclosure comprises a cytokine and either cytokine receptor subunit (see **Table 1**). In some embodiments, a cytokine of the present disclosure will bind its tethered receptor subunit (receptor subunit included with the cytokine in the fusion protein) and then recruit an endogenously expressed second receptor subunit. For example, a fusion protein comprising IFN-β and IFNAR-1 would recruit endogenous IFNAR-2. Alternatively, a fusion protein comprising IFN-β and IFNAR-2 would recruit endogenous IFNAR-1. In some embodiments, a fusion protein of the present disclosure comprises a cytokine and both receptor subunits (e.g., a cytokine selected from **Table 1** and both Receptor 1 and Receptor 2 from the same row in **Table 1**). In some embodiments, a fusion protein of the present disclosure comprising a cytokine and both receptor subunits further comprises a cleavable linker between the receptor subunits.

[0220] In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 80% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 85% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 90% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 95% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 96% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 97% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 98% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 99% identical to a sequence selected from **Table 3a** or **Table 3b**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence identical to a sequence selected from **Table 3a** or **Table 3b**.

[0221] In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a sequence selected from **Table 5a** or **Table 5b**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a sequence selected from **Table 5a** or **Table 5b**.

Signal Peptides

[0222] In some embodiments, a fusion protein of the present disclosure comprises a signal peptide. In some embodiments, a fusion protein of the present disclosure comprises a signal peptide at the N-terminus. In some embodiments, a nucleic acid encoding a signal peptide comprises a nucleic acid encoding a signal peptide. In some embodiments, a signal peptide is or comprises a human signal peptide. In some embodiments, a signal peptide of the present disclosure is from a membrane-expressed or secreted protein. In some embodiments, a signal peptide of the present disclosure is from a membrane-expressed or secreted cytokine. In some embodiments, a signal peptide of the present disclosure is or comprises any signal peptide that

leads to cell membrane localization of an engineered protein. In some embodiments, a signal peptide comprises a CD8 signal peptide.

[0223] In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 80% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 85% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 90% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 95% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 96% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 97% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 98% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence at least 99% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure comprises an amino acid sequence identical to a signal peptide sequence selected from **Table 8**.

[0224] In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 80% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 85% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 90% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 95% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 96% identical to a signal peptide sequence selected from **Table 8**.

In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 97% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 98% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence at least 99% identical to a signal peptide sequence selected from **Table 8**. In some embodiments, a fusion protein of the present disclosure is encoded by one or more nucleic acids comprising a sequence identical to a signal peptide sequence selected from **Table 8**.

Chimeric Antigen Receptors (CAR)

[0225] The term "chimeric antigen receptor" or "CAR," as used herein, refers to an artificial cell surface receptor that is engineered to be expressed on an immune effector cell and specifically targets a cell and/or binds an antigen. CARs may be used, for example, as a therapy with adoptive cell transfer. For example, in some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells are removed from a patient (e.g., from blood, tumor or ascites fluid) and modified so that they express a receptor specific to a particular form of antigen. In some embodiments, such modified immune cells are then reintroduced to the same or a different subject as a therapeutics. In some embodiments, CARs have been expressed with specificity to an antigen, for example, a tumor associated antigen. In some embodiments, a CAR comprises an extracellular domain, a transmembrane domain and an intracellular domain.

[0226] In some embodiments, a modified immune cell, for example, a modified stem cell, macrophage, monocyte, or dendritic cell, is generated by expressing a CAR therein. In some embodiments, an immune cell comprises a CAR comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the immune cell comprises a stem cell, macrophage, monocyte, or dendritic cell.

[0227] In some embodiments, a CAR may further comprise one or more of: one or more extracellular leader domains, one or more extracellular hinge domains and one or more intracellular co-stimulatory domains.

[0228] In some embodiments, a CAR comprises a spacer domain or hinge between an extracellular domain and a transmembrane domain. In some embodiments, a CAR comprises a spacer domain or hinge between an intracellular domain and a transmembrane domain. As used herein, the term "spacer domain" or "hinge" refers to any oligo- or polypeptide that functions to link a transmembrane domain to either an extracellular domain or to an intracellular domain in a polypeptide chain. In some embodiments, a spacer domain or hinge may comprise up to 300 amino acids, preferably 10 to 100 amino acids and most preferably 25 to 50 amino acids. In some embodiments, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length, may form a linkage between a transmembrane domain and an intracellular domain of a CAR. An example of a linker includes a glycine-serine doublet.

[0229] In some embodiments, an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising a CAR may comprise one or more control systems including, but not limited to: a safety switch (e.g., an on switch, and off switch, a suicide switch), a logic gate, for example an AND gate (e.g., two or more CARs, each of which lacks one or more signaling domains such that activation of both/all CARs is required for full immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) activation or function), an OR gate (e.g., two or more CARs, each with an intracellular domain such as CD3ζ and a co-stimulatory domain), and/or a NOT gate (e.g., two or more CARs, one of which includes an inhibitory domain that antagonizes the function of the other CAR[s]).

[0230] The present disclosure also provides immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) comprising a nucleic acid sequence (e.g., an isolated nucleic acid sequence) encoding a CAR, wherein the nucleic acid sequence comprises a nucleic acid sequence encoding an extracellular domain, a nucleic acid sequence encoding a transmembrane domain and a nucleic acid sequence encoding an intracellular domain, wherein the cell is a stem cell, macrophage, monocyte or dendritic cell that expresses the CAR.

[0231] In some embodiments, a CAR comprises an extracellular domain that is operably linked to another domain of the CAR, such as a transmembrane domain or an intracellular domain, for expression in an immune cell. In some embodiments, a nucleic acid encoding an extracellular domain is operably linked to a nucleic acid encoding a transmembrane domain and

the nucleic acid encoding the transmembrane domain is operably linked to a nucleic acid encoding an intracellular domain.

[0232] In some embodiments, an effector activity of an immune cell comprising a CAR is directed against a target cell comprising an antigen that specifically binds an antigen binding domain of the CAR. In some embodiments, a targeted effector activity directed against a target cell is or comprises phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion.

[0233] In some embodiments, a CAR described herein comprises at least one domain (e.g., an extracellular domain, a transmembrane domain, and/or an intracellular domain) that inhibits anti-phagocytic signaling in an immune cell described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell). In some embodiments, a CAR described herein improves effector activity of an immune cell described herein (e.g., a stem cell, macrophage, monocyte, or dendritic cell), e.g., by enhancing inhibition of CD47 and/or SIRPα activity. In some embodiments, a CAR described herein binds CD47, e.g., and serves as a dominant negative receptor, inhibiting SIRPα activity (e.g., a CD47 sink). In some embodiments, a CAR described herein that binds SIRPα, e.g., comprises an activating receptor (e.g., comprises a CD3z intracellular domain). In some embodiments, a CAR described herein inhibits at least one interaction of CD47 and SIRPα. In some embodiments, a CAR is or comprises a phagocytic logic gate.

[0234] In some embodiments, an immune cell described herein (e.g., comprising or expressing an exogenous cytokine, fusion protein and/or a CAR described herein) comprises or expresses at least one variant or fragment of: SIRPα (e.g., a dominant negative SIRPα or a high-affinity engineered variant of SIRPα (e.g., CV1)), 5F9 scFv, B6H12 scFv (e.g., a humanized B6H12 scFv), PD1 (e.g., a dominant negative PD1 or HAC-I), anti-PD1 scFv (e.g., E27 or durvalumab), Siglec-10, Siglec-9, Siglec-11, and/or SHP-1. In some embodiments, a variant or fragment comprises a mutated intracellular domain. In some embodiments, a variant or fragment does not comprise or express at least one intracellular domain (e.g., an immune cell comprises or expresses an anti-CD47 scFv, CD8 hinge domain, and CD8 transmembrane). In some embodiments, an immune cell described herein (e.g., comprising or expressing an exogenous

cytokine, fusion protein and/or a CAR described herein) comprises a dominant negative receptor, e.g., blocking an inhibitory checkpoint.

[0235] In some embodiments, a CAR described herein further comprises a cleavage peptide (e.g., a P2A, F2A, E2A and/or T2A peptide) and at least one second CAR comprising at least one inhibitory domain of anti-phagocytic signaling. In some embodiments, at least one second CAR comprises a SIRPα (e.g., a high-affinity engineered variant of SIRPα (e.g., CV1)), 5F9 scFv, B6H12 scFv (e.g., a humanized B6H12 scFv), or a CD47 binding extracellular domain or a fragment thereof. In some embodiments, at least one second CAR comprises a SIRPα transmembrane domain or a fragment thereof. In certain embodiments, a second CAR further comprises a hinge domain (e.g., a CD8 hinge domain). In certain embodiments, at least one second CAR comprises: (i) a leader sequence (e.g., a CD8 leader); ii) an extracellular domain (e.g., a SIRPα, CV1, 5F9 scFv, or B6H12 scFv (e.g., a humanized B6H12 scFv) extracellular domain); and ii) a transmembrane domain (e.g., a SIRPα transmembrane domain). In some embodiments, a CAR described herein further comprises a cleavage peptide (e.g., a P2A peptide) and at least one marker protein (e.g., CD20 or a fragment thereof, CD19 or a fragment thereof, NGFR or a fragment thereof, a synthetic peptide, and/or a fluorescent protein).

[0236] In some embodiments, an immune cell described herein (e.g., comprising or expressing an exogenous cytokine, fusion protein and/or a CAR described herein) comprises or expresses one or more phosphatase dead domains (e.g. a phosphatase dead Shp1, phosphatase dead 72-5ptase (INPP5E), phosphatase dead Shp2, and/or phosphatase dead SHIP-1 domain) and/or a constitutively active kinase domain (e.g., a constitutively active LYN domain). In some embodiments, a CAR described herein further comprises a cleavage peptide (e.g., a P2A, F2A, E2A and/or T2A peptide) and one or more phosphatase dead domains (e.g. a phosphatase dead Shp1, phosphatase dead 72-5ptase (INPP5E), phosphatase dead Shp2, and/or phosphatase dead SHIP-1 domain) and/or a constitutively active kinase domain (e.g., a constitutively active LYN domain).

Extracellular Domains

[0237] The present disclosure provides chimeric antigen receptors (CAR) comprising extracellular domains. In some embodiments, an extracellular domain comprises an Fc receptor

(FcR) extracellular domain. In some embodiments, an extracellular domain comprises a toll-like receptor (TLR) extracellular domain. In some embodiments, an extracellular domain comprises a leader domain. In some embodiments, an extracellular domain comprises an antigen binding domain. In some embodiments, an extracellular domain comprises a hinge domain. In some embodiments, an extracellular domain comprises one or more of an FcR extracellular domain, a TLR extracellular domain, a leader domain, an antigen binding domain and a hinge domain. In some embodiments, an extracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an extracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein).

FcR Extracellular Domains

[0238] In some embodiments, an FcR extracellular domain comprises a full-length FcR extracellular domain. In some embodiments, an FcR extracellular domain comprises a portion of a full-length FcR extracellular domain. In some embodiments, an FcR extracellular domain (or portion thereof) is or comprises a human FcR extracellular domain. In some embodiments, an FcR extracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR extracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR extracellular domain comprises a CD64 (FcγRI), CD32a (FcγRIIa), CD32b (FcγRIIb), CD32c, CD16a (FcγRIIIa), CD16b (FcγRIIIb), FcεRI, FcεRII, or FcαRI (CD89) domain.

TLR Extracellular Domains

[0239] In some embodiments, a TLR extracellular domain comprises a full-length TLR extracellular domain. In some embodiments, a TLR extracellular domain comprises a portion of a full-length TLR extracellular domain. In some embodiments, a TLR extracellular domain (or portion thereof) is or comprises a human TLR extracellular domain. In some embodiments, a TLR extracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a TLR extracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a

modified immune cell as provided herein). In some embodiments, a TLR extracellular domain comprises a TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, or TLR9 domain.

Leader Domains

[0240] In some embodiments, a CAR comprises one or more extracellular leader domains. In some embodiments, a nucleic acid encoding a CAR comprises a nucleic acid sequence encoding an extracellular leader domain, but the extracellular leader domain is cleaved from the CAR before the CAR is expressed in an immune cell. In some embodiments, an extracellular leader domain is or comprises a human extracellular leader domain. In some embodiments, an extracellular leader domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an extracellular leader domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an extracellular leader domain comprises a CD8 extracellular leader domain. In some embodiments, an extracellular leader domain comprises a leader domain from a stimulatory or co-stimulatory domain (e.g., a TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, ALK, AXL, DDR2, EGFR, EphA1, INSR, cMET, MUSK, PDGFR, PTK7, RET, ROR1, ROS1, RYK, TIE2, TRK, VEGFR, CD40, CD19, CD20, 41BB, CD28, OX40, GITR, TREM-1, TREM-2, DAP12, MR, ICOS, MyD88 domain).

Antigen Binding Domains

[0241] In some embodiments, a CAR comprises an antigen binding domain that binds to an antigen, for example, on a target cell. In some embodiments, a CAR comprises an antigen binding domain that binds to an antigen associated with viral infection, bacterial infection, parasitic infection, autoimmune disease, and/or cancer cells. In some embodiments, an antigen binding domain recognizes an antigen that acts as a cell surface marker on a target cell associated with a particular disease state.

[0242] In some embodiments, an antigen binding domain binds to a tumor antigen, such as an antigen that is specific for a tumor or cancer of interest. In some embodiments a tumor antigen comprises one or more antigenic cancer epitopes. In some embodiments, a tumor antigen comprises CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1);

CD33; epidermal growth factor receptor variant III (EGFRvIII); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAcα-Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms-Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma-associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein-coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycoceramide (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-

associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; surviving; telomerase; prostate carcinoma tumor antigen-1 (PCTA-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1 (CYP1B1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); or immunoglobulin lambda-like polypeptide 1 (IGLL1). In certain embodiments, a tumor antigen comprises ERBB2 (Her2/neu). In certain embodiments, a tumor antigen comprises PSMA. In certain embodiments, a tumor antigen comprises Mesothelin.

[0243] In some embodiments, an antigen binding domain binds to a misfolded protein antigen or a protein of a protein aggregate, such as a protein that is specific for a disease/disorder of interest. In some embodiments, the disease/disorder is a neurodegenerative disease/disorder,

an inflammatory disease/disorder, a cardiovascular disease/disorder, a fibrotic disease/disorder, or amyloidosis (e.g., mediated by protein aggregates of immunoglobulin light chains or of transthyretin). In some embodiments, the neurodegenerative disease/disorder is selected from the group consisting of tauopathy, asynucleopathy, presenile dementia, senile dementia, Alzheimer's disease (mediated by protein aggregates ofbeta-amyloid), Parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP), Pick' s disease, primary progressive aphasia, frontotemporal dementia, corticobasal dementia, Parkinson's disease, Parkinson's disease with dementia, dementia with Lewy bodies, Down syndrome, multiple system atrophy, amyotrophic lateral sclerosis (ALS), Hallervorden-Spatz syndrome, polyglutamine disease, trinucleotide repeat disease, Familial British dementia, Fatal Familial Insomnia, Gerstmann-Straussler-Scheinker Syndrome, Hereditary cerebral hemorrhage with amyloidosis (Icelandic) (HCHW A-I), Sporadic Fatal Insomnia (sFI), Variably Protease-Sensitive Prionopathy (VPSPr), Familial Danish dementia, and prion disease (such as Creutzfeldt-Jakob disease, CJD and Variant Creutzfeldt-Jakob Disease (vCJD)).

[0244] In some embodiments, an antigen binding domain comprises any domain that binds to an antigen. In some embodiments, an antigen binding domain is or comprises a monoclonal antibody, a polyclonal antibody, a synthetic antibody, a human antibody, a humanized antibody, a non-human antibody, or any fragment thereof, for example an scFv. In some embodiments, an antigen binding domain is or comprises an aptamer, a darpin, a centyrin, a naturally occurring or synthetic receptor, an affibody, or other engineered protein recognition molecule. In some embodiments, an antigen binding domain is or comprises a mammalian antibody or a fragment thereof. In some embodiments, an antigen binding domain is derived, in whole or in part, from the same species in which the CAR will ultimately be used. For example, for use in humans, an antigen binding domain of a CAR comprises a human antibody, a humanized antibody, or a fragment thereof (e.g. a scFv). In some embodiments, an antigen binding domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an antigen binding domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein).

[0245] In some embodiments, a CAR comprises one or more antigen binding domains. In some embodiments, a CAR comprises two or more antigen binding domains. In some embodiments, a CAR is a bispecific CAR. In some embodiments, an immune cell comprises two or more different CARs comprising one or more antigen binding domains. In some embodiments, an immune cell comprising a bispecific CAR and/or comprising two or more different CARs comprising one or more antigen binding domains can reduce off-target and/or on-target off-tissue effects by requiring that two antigens are present. In some embodiments, an immune cell comprises a bispecific CAR and/or comprises two or more different CARs comprising one or more antigen binding domains, wherein the CARs provide distinct signals that in isolation are insufficient to mediate activation of the modified cell, but are synergistic together, stimulating activation of the modified cell. In some embodiments, such a construct may be referred to as an 'AND' logic gate.

[0246] In some embodiments, an immune cell comprising a bispecific CAR and/or comprising two or more different CARs comprising one or more antigen binding domains can reduce off-target and/or on-target off-tissue effects by requiring that one antigen is present and a second, normal protein antigen is absent before the cell's activity is stimulated. In some embodiments, such a construct may be referred to as a 'NOT' logic gate. In contrast to AND gates, NOT gated CAR-modified cells are activated by binding to a single antigen. However, the binding of a second receptor to the second antigen functions to override the activating signal being perpetuated through the CAR. Typically, such an inhibitory receptor would be targeted against an antigen that is abundantly expressed in a normal tissue but is absent in tumor tissue.

Hinge Domains

[0247] In some embodiments, a CAR comprises one or more extracellular hinge domains. In some embodiments, an extracellular hinge domain is or comprises a human extracellular hinge domain. In some embodiments, an extracellular hinge domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an extracellular hinge domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, one or more extracellular hinge domains comprise a CD8a extracellular hinge domain or an IgG4 or a CD28 extracellular hinge domain. In some

embodiments, an extracellular hinge domain optimizes the physicochemical parameters of a CAR, e.g., optimal size relative to tumor antigen (e.g., allowing for exclusion of inhibitory molecules), optimal flexibility, optimal protein folding, optimal protein stability, optimal binding, optimal homodimerization, and/or lack of homodimerization.

Transmembrane Domains

[0248] In some embodiments, a CAR comprises a transmembrane domain, for example, that connects an extracellular domain to an intracellular domain. In some embodiments, a transmembrane domain is naturally associated with one or more other domain(s) of a CAR. In some embodiments, a transmembrane domain can be modified to avoid binding to transmembrane domains of other surface membrane proteins, in order to minimize interactions with other members of a receptor complex. In some embodiments, a transmembrane domain may be derived either from a naturally-occurring or from a synthetic source. In some embodiments a transmembrane domain is derived from a naturally-occurring membrane-bound or transmembrane protein. In some embodiments, a transmembrane domain is or comprises a human transmembrane domain. In some embodiments, a transmembrane domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a transmembrane domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a transmembrane domain comprises a CD8a, CD64, CD32a, CD32c, CD16a, TRL1, TLR2, TLR3, TRL4, TLR5, TLR6, TLR7, TLR8, TLR9, ALK, AXL, DDR2, EGFR, EphA1, INSR, cMET, MUSK, PDGFR, PTK7, RET, ROR1, ROS1, RYK, TIE2, TRK, VEGFR, CD40, CD19, CD20, 41BB, CD28, OX40, GITR, TREM-1, TREM-2, DAP12, MR, ICOS, MyD88, CD3-zeta, FcR γ, V/I/LxYxxL/V, SIRPα, CD45, Siglec-10, PD1, SHP-1, SHP-2, KIR-2DL, KIR-3DL, NKG2A, CD170, CD33, BTLA, CD32b, SIRPβ, CD22, PIR-B, LILRB1, CD36, or Syk transmembrane domain.

FcR Transmembrane Domains

[0249] In some embodiments, an FcR transmembrane domain comprises a full-length FcR transmembrane domain. In some embodiments, an FcR transmembrane domain comprises a portion of a full-length FcR transmembrane domain. In some embodiments, an FcR

transmembrane domain is or comprises a human FcR transmembrane domain, or portion thereof. In some embodiments, an FcR transmembrane domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR transmembrane domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR transmembrane domain comprises a CD64 (FcγRI), CD32a (FcγRIIa), CD32b (FcγRIIb), CD32c, CD16a (FcγRIIIa), CD16b (FcγRIIIb), FcεRI, FcεRII, or FcαRI (CD89) domain.

TLR Transmembrane Domains

[0250] In some embodiments, a TLR transmembrane domain comprises a full-length TLR transmembrane domain. In some embodiments, a TLR transmembrane domain comprises a portion of a full-length TLR transmembrane domain. In some embodiments, a TLR transmembrane domain is or comprises a human TLR transmembrane domain, or portion thereof. In some embodiments, a TLR transmembrane domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a TLR transmembrane domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a TLR transmembrane domain comprises a TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, or TLR9 domain.

Intracellular Domains

[0251] In some embodiments, a CAR comprises one or more intracellular domains. In some embodiments, an intracellular domain is or comprises a human intracellular domain, or portion thereof. In some embodiments, an intracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an intracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an intracellular domain and/or other cytoplasmic domain of a CAR is responsible for activation of the cell in which the CAR is expressed (e.g., an immune cell). In some

embodiments, an intracellular domain of a CAR is responsible for signal activation and/or transduction in an immune cell comprising said CAR.

[0252] In some embodiments, an intracellular domain of a CAR includes at least one domain responsible for signal activation and/or transduction. In some embodiments, an intracellular domain is or comprises at least one of a co-stimulatory molecule and a signaling domain. In some embodiments, an intracellular domain of a CAR comprises dual signaling domains. In some embodiments, an intracellular domain of a CAR comprises more than two signaling domains.

[0253] In some embodiments, an intracellular domain comprises a cytoplasmic portion of a surface receptor. In some embodiments, an intracellular domain comprises a co-stimulatory molecule. In some embodiments, an intracellular domain comprises a molecule that acts to initiate signal transduction in an immune cell.

[0254] In some embodiments, an intracellular domain of a CAR includes any portion of one or more co-stimulatory molecules, such as at least one signaling domain from CD3, Fc epsilon RI gamma chain, any derivative or variant thereof, any synthetic sequence thereof that has the same functional capability, and any combination thereof.

FcR Intracellular Domains

[0255] In some embodiments, an FcR intracellular domain comprises a full-length FcR intracellular domain. In some embodiments, an FcR intracellular domain comprises a portion of a full-length FcR intracellular domain. In some embodiments, an FcR intracellular domain is or comprises a human FcR intracellular domain, or portion thereof. In some embodiments, an FcR intracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR intracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, an FcR intracellular domain comprises a CD64 (FcγRI), CD32a (FcγRIIa), CD32b (FcγRIIb), CD32c, CD16a (FcγRIIIa), CD16b (FcγRIIIb), FcεRI, FcεRII, or FcαRI (CD89) domain.

TLR Intracellular Domains

[0256] In some embodiments, a TLR intracellular domain comprises a full-length TLR intracellular domain. In some embodiments, a TLR intracellular domain comprises a portion of a full-length TLR intracellular domain. In some embodiments, a TLR intracellular domain is or comprises a human TLR intracellular domain, or portion thereof. In some embodiments, a TLR intracellular domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a TLR intracellular domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a TLR intracellular domain comprises a TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, or TLR9 domain.

Signaling Domains

[0257] In some embodiments, a CAR comprises one or more intracellular signaling domains. In some embodiments, an intracellular signaling domain is or comprises a human intracellular signaling domain, or portion thereof. In some embodiments, a signaling domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a signaling domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein).

[0258] In some embodiments, one or more intracellular signaling domains comprise a CD3-zeta, FcR γ, CD64, CD32a, CD32c, CD16a, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, ALK, AXL, DDR2, EGFR, EphA1, INSR, cMET, MUSK, PDGFR, PTK7, RET, ROR1, ROS1, RYK, TIE2, TRK, VEGFR, CD40, CD19, CD20, 41BB, CD28, OX40, GITR, TREM-1, TREM-2, DAP12, MR, ICOS, MyD88, V/I/LxYxxL/V, SIRPα, CD45, Siglec-10, PD1, SHP-1, SHP-2, KIR-2DL, KIR-3DL, NKG2A, CD170, CD33, BTLA, CD32b, SIRPβ, CD22, PIR-B, LILRB1,Syk, 41BB ligand (41BBL; TNFSF9), CD27, OX40L, CD32b, CD11b, ITGAM, SLAMF7, CD206, CD163, CD209, Dectin-2, or one or more cytokine receptor signaling domains (e.g., an IL1R, an IL2R, an IL3R, an IL4R, an IL5R, an IL6R, an IL7R, an IL8R, an IL9R, an IL10R, an IL11R, an IL12R, an IL13R, an IL14R, an IL15R, an IL17R, an IFNaR, an IFNgR, an TNFR, an CSF1R, an CSF2R, Dap10, CD36, Dectin-1, or ICOSL intracellular signaling domain)

[0259] In some embodiments, an intracellular domain of a CAR comprises dual signaling domains, such as 41BB, CD28, ICOS, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8,

TLR9, TLR10, TLR11, CD116 receptor beta chain, CSF1-R, LRP1/CD91, SR-A1, SR-A2, MARCO, SR-CL1, SR-CL2, SR-C, SR-E, CR1, CR3, CR4, dectin 1, DEC-205, DC-SIGN, CD14, CD36, LOX-1, CD11b, together with any of the signaling domains listed in the above paragraph in any combination.

Co-stimulatory Domains

[0260] As used herein, a "co-stimulatory molecule" or "co-stimulatory domain" refers to a molecule in an immune cell that is used to heighten or dampen an initial stimulus. For example, pathogen-associated pattern recognition receptors, such as TLR or the CD47/SIRPα axis, are molecules on immune cells that, respectively, heighten or dampen an initial stimulus. In some embodiments, a co-stimulatory domain comprises TCR, CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, CD86, common FcR gamma, FcR beta (Fc Epsilon R1b), CD79a, CD79b, Fcgamma RIIa, DAP10, DAP12, T cell receptor (TCR), CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD127, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, other co-stimulatory molecules described herein, any derivative, variant, or fragment thereof, any synthetic sequence of a co-stimulatory molecule that has the same functional capability, and any combinations thereof.

[0261] In some embodiments, a co-stimulatory domain may be a domain that is endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein). In some embodiments, a co-stimulatory domain may be a domain that is not endogenous to a particular immune cell type (e.g., a modified immune cell as provided herein).

[0262] As used herein, a "co-stimulatory signal" refers to a signal, which in combination with a primary signal, such as activation of a CAR on an immune cell, leads to activation of the immune cell.

Cleavage Peptides

[0263] As used herein, a cleavage peptide refers to a peptide that can induce the cleaving of a recombinant protein in a cell. In some embodiments, a cleavage peptide is a 2A peptide. In some embodiments, a cleavage peptide is or comprises a P2A, F2A, E2A or T2A peptide. In some embodiments, a nucleic acid as described herein comprises one or more nucleic acid sequences encoding one or more cleavage peptides. In some embodiments, a nucleic acid comprising a nucleic acid sequence encoding a cleavage peptide also comprises one or more nucleic acid sequences encoding one or more intracellular domains and one or more nucleic acid sequences comprising one or more peptide agents, wherein translation of the nucleic acid results in a protein comprising one or more intracellular domains separated from one or more peptide agents by a cleavage peptide. In some embodiments, a first promoter is operably linked to one or more nucleic acids encoding a CAR and a second promoter is operably linked to one or more nucleic acids encoding a peptide agent. In some embodiments, a nucleic acid sequence comprising a CAR, and optionally one or more peptide agents, further comprises an internal ribosome entry site (IRES) sequence. An IRES sequence may be any viral, chromosomal or artificially designed sequence that initiates cap-independent ribosome binding to mRNA facilitates the initiation of translation.

Peptide Agents

[0264] As used herein, a peptide agent refers to a peptide co-expressed with a CAR in an immune cell. In some embodiments, a peptide agent is co-expressed with a CAR to ensure stoichiometric balance and optimal signaling of a CAR. In some embodiments, a peptide agent forms a homodimer with an identical peptide agent. In some embodiments, a peptide agent forms a heterodimer with a different peptide agent. In some embodiments, a nucleic acid as described herein comprises one or more nucleic acid sequences encoding one or more peptide agents. In some embodiments, a peptide agent is or comprises an FcR gamma chain.

[0265] In some embodiments, a peptide agent comprises any peptide, protein, receptor, secreted antibody or a fragment thereof (e.g., an scFv, Fab, Fab', F(ab')2, Fc, or nanobody). In

some embodiments, a peptide agent comprises one or more cytokines (e.g., one or more of IL-1, IL-2, IL-6, IL-8, TNF-a, IFNa, IFNb, IFN-y, GMCSF, or MCSF), CD40-L, dominant negative SIRPα, dominant negative PD1, dominant negative CD45, dominant negative SIGLEC 10, or dominant negative LILRB.

Fc Receptors (FcR)

[0266] In some embodiments, a CAR comprises one or more antigen binding domains and an FcR extracellular domain, and/or the transmembrane domain of the CAR comprises an FcR transmembrane domain, and/or the intracellular domain of the CAR comprises an FcR intracellular domain. In some embodiments, a CAR comprises, from N-terminus to C-terminus, one or more extracellular binding domains, an FcR extracellular domain, an FcR transmembrane domain, and an FcR intracellular domain. In some embodiments, one or more of the FcR extracellular domain, the FcR transmembrane domain and the FcR intracellular domain is or comprises a human FcR domain. In some embodiments, an FcR extracellular domain, an FcR transmembrane domain and an FcR intracellular domain together comprise a full-length FcR. In some embodiments, an FcR extracellular domain, an FcR transmembrane domain and an FcR intracellular domain together comprise a portion of a full-length FcR. In some embodiments, an FcR extracellular domain comprises a portion of a full-length FcR extracellular domain. In some embodiments, an FcR transmembrane domain comprises a portion of a full-length FcR transmembrane domain. In some embodiments, an FcR intracellular domain comprises a portion of a full-length FcR intracellular domain.

Toll-Like Antigen Receptors (TLR)

[0267] In some embodiments, a CAR comprises one or more antigen binding domains and a toll-like receptor (TLR) extracellular domain and/or the transmembrane domain of the CAR comprises a TLR transmembrane domain and/or the intracellular domain of the CAR comprises a TLR intracellular domain. In some embodiments, a CAR comprises, from N-terminus to C-terminus, one or more extracellular binding domains, a TLR extracellular domain, a TLR transmembrane domain, and a TLR intracellular domain. In some embodiments, one or more of the TLR extracellular domain, the TLR transmembrane domain and the TLR

intracellular domain is or comprises a human TLR domain. In some embodiments, a TLR extracellular domain, a TLR transmembrane domain and a TLR intracellular domain together comprise a full-length TLR. In some embodiments, a TLR extracellular domain, a TLR transmembrane domain and a TLR intracellular domain together comprise portion of a full-length TLR. In some embodiments, a TLR extracellular domain comprises a portion of a full-length TLR extracellular domain. In some embodiments, a TLR transmembrane domain comprises a portion of a full-length TLR transmembrane domain. In some embodiments, a TLR intracellular domain comprises a portion of a full-length TLR intracellular domain.

Nucleic Acid Constructs

[0268] The present disclosure provides, among other things, nucleic acid molecules encoding at least one exogenous cytokine described herein or a fragment thereof. The present disclosure provides, among other things, nucleic acid molecules encoding at least one fusion protein described herein or a fragment thereof. In some embodiments, the present disclosure provides nucleic acid molecules encoding at least one CAR described herein or a fragment thereof. An immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) can comprise a nucleic acid molecule (e.g., an exogenous nucleic acid molecule) encoding at least one protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) described herein. In some embodiments, a nucleic acid molecule encoding at least one fusion protein comprises a cytokine and a cytokine receptor.

[0269] Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase "nucleotide sequence that encodes a protein or an RNA" may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s). The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to

that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0270] The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the heterologous nucleic acid sequence. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, e.g., where necessary to join two protein coding regions, are in the same reading frame.

[0271] Nucleic acid molecules encoding at least one protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) described herein or a fragment thereof can be a DNA molecule, an RNA molecule, or a combination thereof. In some embodiments, a nucleic acid molecule comprises or is a messenger RNA (mRNA) transcript encoding at least one protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) described herein or a fragment thereof. In some embodiments, a nucleic acid molecule comprises or is a DNA construct encoding at least one protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) described herein or a fragment thereof.

[0272] In some embodiments, all or a fragment of a protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) described herein is encoded by a codon optimized nucleic acid molecule, e.g., for expression in a cell (e.g., a mammalian cell). A variety of codon optimization methods are known in the art, e.g., as disclosed in US Patent Nos. 5,786,464 and 6,114,148, each of which is hereby incorporated by reference in its entirety.

[0273] Expression of nucleic acids as described herein may be achieved by operably linking a nucleic acid encoding a protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) or fragment thereof to a promoter in an expression vector. Exemplary promoters (e.g., constitutive promoters) include, but are not limited to, an elongation factor-1α promoter (EF-1α) promoter, immediate early cytomegalovirus (CMV) promoter, ubiquitin C promoter, phosphoglycerokinase (PGK) promoter, simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV) promoter, human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, Moloney murine leukemia virus (MoMuLV) promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, an actin promoter, a myosin promoter, a hemoglobin promoter, or a creatine kinase promoter. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter. A vector can also comprise additional promoter elements, e.g., enhancers, to regulate the frequency of transcriptional initiation.

[0274] In some embodiments, a vector comprising a nucleic acid molecule encoding a protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) or fragment thereof comprises or is a viral vector. Viral vector technology is well known in the art and is described (e.g., in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1-4, Cold Spring Harbor Press, NY). Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated viral vectors, or retroviral vectors (e.g., a lentiviral vector or a gammaretroviral vector). In some embodiments, a vector comprises a lentiviral vector (e.g., as described in US Patent No. 9,149,519 or International Publication No. WO 2017/044487, each of which is hereby incorporated by reference in its entirety).

[0275] In some embodiments, a viral vector comprises an adenoviral vector. Adenoviruses are a large family of viruses containing double stranded DNA. They replicate within the nucleus of a host cell, using the host's cell machinery to synthesize viral RNA, DNA and proteins. Adenoviruses are known in the art to affect both replicating and non-replicating cells, to accommodate large transgenes, and to code for proteins without integrating into the host

cell genome. In some embodiments, an adenoviral vector comprises an Ad2 vector or an Ad5 vector (e.g., Ad5f35 adenoviral vector, e.g., a helper-dependent Ad5F35 adenoviral vector).

[0276] In some embodiments, a viral vector is an adeno-associated virus (AAV) vector. AAV systems are generally well known in the art (see, e.g., Kelleher and Vos, Biotechniques, 17(6):1110-17 (1994); Cotten et al., P.N.A.S. U.S.A., 89(13):6094-98 (1992); Curiel, Nat Immun, 13(2-3):141-64 (1994); Muzyczka, Curr Top Microbiol Immunol, 158:97-129 (1992); and Asokan A, et al., Mol. Ther., 20(4):699-708 (2012)). Methods for generating and using recombinant AAV (rAAV) vectors are described, for example, in U.S. Pat. Nos. 5,139,941 and 4,797,368.

[0277] Several AAV serotypes have been characterized, including AAV1, AAV2, AAV3 (e.g., AAV3B), AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAV11, as well as variants thereof. Generally, any AAV serotype may be used to deliver a protein (e.g., an exogenous cytokine of the present disclosure, a fusion protein of the present disclosure or a CAR of the present disclosure) or fragment thereofdescribed herein. In some embodiments, an AAV serotype has a tropism for a particular tissue.

[0278] In some embodiments, CRISPR/Cas9 system has recently been shown to facilitate high levels of precise genome editing using adeno associated viral (AAV) vectors to serve as donor template DNA during homologous recombination (HR).

[0279] In some embodiments, a vector comprises a gammaretroviral vector (e.g., as described in Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" Viruses. 2011 Jun; 3(6): 677–713, which is hereby incorporated by reference in its entirety). Exemplary gammaretroviral vectors include Murine Leukemia Virus (MLV), Spleen-Focus Forming Virus (SFFV), and Myeloproliferative Sarcoma Virus (MPSV), and vectors derived therefrom.

[0280] In some embodiments, a vector comprises two or more nucleic acid sequences encoding proteins, e.g., at least one exogenous cytokine described herein and a CAR described herein. In some embodiments, a vector comprises two or more nucleic acid sequences encoding proteins, e.g., at least one fusion protein described herein, and a CAR described herein. In some embodiments, two or more nucleic acid sequences encoding an exogenous cytokine and a CAR are encoded by a single nucleic molecule, e.g., in same frame and as a single polypeptide chain.

In some embodiments, two or more nucleic acid sequences encoding a fusion protein and a CAR are encoded by a single nucleic molecule, e.g., in same frame and as a single polypeptide chain. In some embodiments, two or more proteins (e.g., an exogenous cytokine and a CAR) are separated by one or more cleavage peptide sites (e.g., an auto-cleavage site or a substrate for an intracellular protease). In some embodiments, two or more proteins (e.g., a fusion protein and a CAR) are separated by one or more cleavage peptide sites (e.g., an auto-cleavage site or a substrate for an intracellular protease). In certain embodiments, a cleavage peptide comprises a porcine teschovirus-l (P2A) peptide, Thosea asigna virus (T2A) peptide, equine rhinitis A virus (E2A) peptide, foot-and-mouth disease virus (F2A) peptide, or a variant thereof.

[0281] In some embodiments, a vector comprises at least one nucleic acid sequence encoding a protein, e.g., at least one exogenous cytokine described herein, at least one fusion protein described herein or at least one CAR described herein, and at least one nucleic acid encoding at least one gene co-expressed with a second protein, e.g., a cytokine described herein (e.g., TNF, IL-12, IFN, GM-CSF, G-CSF, M-CSF, and/or IL-1) or a stimulatory ligand described herein (e.g., CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, ICOS-L, ICAM, CD30L, CD40, CD40L, CD70, CD83, HLA-G, MICA, MICB, HVEM, lymphotoxin beta receptor, 3/TR6, ILT3, ILT4, HVEM, an agonist or antibody that binds Toll ligand receptor, and/or a B7-H3 ligand).

Pharmaceutical Compositions

[0282] The present disclosure, among other things, provides pharmaceutical compositions comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents, or excipients.

[0283] When "a therapeutically effective amount, "an immunologically effective amount," "an anti-immune response effective amount," or "an immune response-inhibiting effective amount" is indicated, a precise amount of a pharmaceutical composition comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) can be determined by a physician with consideration of individual differences in age, weight, immune response, and condition of the patient (subject).

[0284] Pharmaceutical compositions comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) may comprise buffers, such as neutral buffered saline or phosphate buffered saline (PBS); carbohydrates, such as glucose, mannose, sucrose, dextrans, or mannitol; proteins, polypeptides, or amino acids (e.g., glycine); antioxidants; chelating agents, such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); serum and preservatives, such as cryoprotectant. In some embodiments, a pharmaceutical composition is substantially free of contaminants, e.g., there are no detectable levels of a contaminant (e.g., an endotoxin).

[0285] Pharmaceutical compositions described herein may be administered in a manner appropriate to the disease, disorder, or condition to be treated or prevented. Quantity and frequency of administration will be determined by such factors as condition of a patient, and type and severity of a patient's disease, disorder, or condition, although appropriate dosages may be determined by clinical trials.

[0286] Pharmaceutical compositions described herein may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, liposomes, and suppositories. Preferred compositions may be injectable or infusible solutions. Pharmaceutical compositions described herein can be formulated for administration intravenously, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, transarterially, or intraperitoneally.

[0287] In some embodiments, a pharmaceutical composition described herein is formulated for parenteral (e.g., intravenous, subcutaneous, intraperitoneal, or intramuscular) administration. In some embodiments, a pharmaceutical composition described herein is formulated for intravenous infusion or injection. In some embodiments, a pharmaceutical composition described herein is formulated for intramuscular or subcutaneous injection. Pharmaceutical compositions described herein can be formulated for administered by using infusion techniques that are commonly known in immunotherapy (See, e.g., Rosenberg et al., New Eng. J. of Med. 319:1676, 1988, which is hereby incorporated by reference in its entirety).

[0288] As used herein, the terms "parenteral administration" and "administered parenterally" refer to modes of administration other than enteral and topical administration,

usually by injection or infusion, and include, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intratumoral, and intrasternal injection and infusion.

[0289] Pharmaceutical compositions comprising immune cells as described herein may be administered at a dosage of about 104 to about 109 cells/kg body weight (e.g., about 105 to about 106 cells/kg body weight), including all integer values within those ranges. In some embodiments, a dose of immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) comprises at least about 1 x 106, about 1.1 x 106, about 2 x 106, about 3.6 x 106, about 5 x 106, about 1 x 107, about 1.8 x 107, about 2 x 107, about 5 x 107, about 1 x 108, about 2 x 108, about 5 x 108, about 1 x 109, about 2 x 109, or about 5 x 109 cells. Pharmaceutical compositions described herein may also be administered multiple times at a certain dosage. An optimal dosage and treatment regime for a particular patient can readily be determined by one skilled in the art by monitoring a patient for signs of a disease, disorder, or condition and adjusting treatment accordingly.

[0290] It may be desired to administer pharmaceutical compositions comprising immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein to a subject and then subsequently redraw blood (or have apheresis performed), activate collected immune cells, and reinfuse a subject with activated immune cells. This process can be performed multiple times, e.g., every few weeks. Immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) can be activated from blood draws of from about 10 cc to about 400 cc. In some embodiments, immune cells (e.g., macrophages, monocytes, or dendritic cells) are activated from blood draws of about 20 cc, about 30 cc, about 40 cc, about 50 cc, about 60 cc, about 70 cc, about 80 cc, about 90 cc, or about 100 cc. Without being bound by theory, methods comprising multiple blood draw and reinfusions as described herein may select for certain immune cell populations. In some embodiments, pharmaceutical compositions comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) are administered in combination with (e.g., before, simultaneously, or following) a second therapy. For example, a second therapy can include, but is not limited to antiviral therapy (e.g., cidofovir, interleukin-2, Cytarabine (ARA-C), or natalizumab), chimeric antigen

receptor-T cell (CAR-T) therapy, T-cell receptor (TCR)-T cell therapy, chemotherapy, radiation, an immunosuppressive agent (e.g., cyclosporin, azathioprine, methotrexate, mycophenolate, FK506 antibody, or glucocorticoids), an antagonist (e.g., one or more of a PD-1 antagonist, a PD-L1 antagonist, CTLA4 antagonist, CD47 antagonist, SIRPα antagonist, CD40 agonists, CSF1/CSF1R antagonist, or a STING agonist), or an immunoablative agent (e.g., an anti-CD52 antibody (e.g., alemtuzumab), an anti-CD3 antibody, cytoxin, fludaribine, cyclosporin, FK506, rapamycin, mycophenolic acid, a steroid, FR901228, or irradiation).

[0291] In some embodiments, pharmaceutical compositions comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) are administered in combination with (e.g., before, simultaneously, or following) bone marrow transplantation or lymphocyte ablative therapy using a chemotherapy agent (e.g., fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or Rituxan). In certain embodiments, subjects undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following transplant, subjects receive an infusion of a pharmaceutical composition comprising immune cells as described herein. Pharmaceutical compositions described herein may be administered before or following surgery.

[0292] A dosage of any aforementioned therapy to be administered to a subject will vary with a disease, disorder, or condition being treated and based on a specific subject. Scaling of dosages for human administration can be performed according to art-accepted practices. For example, a dose of alemtuzumab will generally be about 1 mg to about 100 mg for an adult, usually administered daily for a period of between about 1 day to about 30 days, e.g., a daily dose of about 1 mg to about 10 mg per day (e.g., as described in U.S. Patent No. 6,120,766, which is hereby incorporated by reference in its entirety).

Methods of Treatment

[0293] The present disclosure, among other things, provides methods of treating a disease or disorder (e.g., a disease or a disorder described herein) in a subject comprising delivering a pharmaceutical composition comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells). In some embodiments, a therapeutically effective amount of a pharmaceutical composition described herein is administered to a subject

having a disease or disorder. Pharmaceutical compositions as described herein can be for use in the manufacture of a medicament for treating a disease or disorder in a subject or stimulating an immune response in a subject.

[0294] A subject to be treated with methods described herein can be a mammal, e.g., a primate, e.g., a human (e.g., a patient having, or at risk of having, a disease or disorder described herein). In some embodiments, immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) may be autologous, allogeneic, or xenogeneic with respect to a subject. Pharmaceutical compositions as described herein can be administered to a subject in accordance with a dosage regimen described herein, alone or in combination with one or more therapeutic agents, procedures, or modalities.

[0295] Pharmaceutical composition comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) can be used to treat or prevent a disease associated with a tumor or cancer, a neurodegenerative disease or disorder, an inflammatory disease or disorder, a cardiovascular disease or disorder, a fibrotic disease or disorder, a disease associated with amyloidosis, and a combination of thereof.

[0296] A method of treating (e.g., one or more of reducing, inhibiting, or delaying progression of) a cancer or a tumor in a subject with a pharmaceutical composition comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) is provided. A subject can have an adult or pediatric form of cancer. A cancer may be at an early, intermediate, or late stage, or a metastatic cancer. A cancer can include, but is not limited to, a solid tumor, a hematological cancer (e.g., leukemia, lymphoma, or myeloma, e.g., multiple myeloma), or a metastatic lesion. Examples of solid tumors include malignancies, e.g., sarcomas and carcinomas, e.g., adenocarcinomas of the various organ systems, such as those affecting the lung, breast, ovarian, lymphoid, gastrointestinal (e.g., colon), anal, genitals and genitourinary tract (e.g., renal, urothelial, bladder cells, prostate), pharynx, CNS (e.g., brain, neural or glial cells), head and neck, skin (e.g., melanoma, e.g., a cutaneous melanoma), pancreas, and bones (e.g., a chordoma).

[0297] In some embodiments, a cancer is chosen from a lung cancer (e.g., a non-small cell lung cancer (NSCLC) (e.g., a non-small cell lung cancer (NSCLC) with squamous and/or non-squamous histology, or a NSCLC adenocarcinoma), or a small cell lung cancer (SCLC)), a

skin cancer (e.g., a Merkel cell carcinoma or a melanoma (e.g., an advanced melanoma)), an ovarian cancer, a mesothelioma, a bladder cancer, a soft tissue sarcoma (e.g., a hemangiopericytoma (HPC)), a bone cancer (a bone sarcoma), a kidney cancer (e.g., a renal cancer (e.g., a renal cell carcinoma)), a liver cancer (e.g., a hepatocellular carcinoma), a cholangiocarcinoma, a sarcoma, a myelodysplastic syndrome (MDS), a prostate cancer, a breast cancer (e.g., a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, e.g., a triple negative breast cancer), a colorectal cancer (e.g., a relapsed colorectal cancer or a metastatic colorectal cancer, e.g., a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer), a nasopharyngeal cancer, a duodenal cancer, an endometrial cancer, a pancreatic cancer, a head and neck cancer (e.g., head and neck squamous cell carcinoma (HNSCC)), an anal cancer, a gastro-esophageal cancer, a thyroid cancer (e.g., anaplastic thyroid carcinoma), a cervical cancer (e.g., a squamous cell carcinoma of the cervix), a neuroendocrine tumor (NET) (e.g., an atypical pulmonary carcinoid tumor), a lymphoproliferative disease (e.g., a post-transplant lymphoproliferative disease), a lymphoma (e.g., T-cell lymphoma, B-cell lymphoma, or a non-Hodgkin lymphoma), a myeloma (e.g., a multiple myeloma), or a leukemia (e.g., a myeloid leukemia or a lymphoid leukemia).

[0298] In some embodiments, a cancer is a brain tumor, e.g., a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments, a cancer is a pancreatic cancer, e.g., an advanced pancreatic cancer. In some embodiments, a cancer is a skin cancer, e.g., a melanoma (e.g., a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In some embodiments, a cancer is a renal cancer, e.g., a renal cell carcinoma (RCC) (e.g., a metastatic renal cell carcinoma). In some embodiments, a cancer is a breast cancer, e.g., a metastatic breast carcinoma or a stage IV breast carcinoma, e.g., a triple negative breast cancer (TNBC). In some embodiments, a cancer is a virus-associated cancer. In some embodiments, a cancer is an anal canal cancer (e.g., a squamous cell carcinoma of the anal canal). In some embodiments, a cancer is a cervical cancer (e.g., a squamous cell carcinoma of the cervix). In some embodiments, a cancer is a gastric cancer (e.g., an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma). In some embodiments, a cancer is a head and neck cancer (e.g., an HPV positive and negative squamous cell cancer of the head and neck

(SCCHN)). In some embodiments, a cancer is a nasopharyngeal cancer (NPC). In some embodiments, a cancer is a colorectal cancer, e.g., a relapsed colorectal cancer, a metastatic colorectal cancer, e.g., a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer.

[0299] In some embodiments, a cancer is a hematological cancer. In some embodiments, a cancer is a leukemia, e.g., acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic leukemia, or acute leukemia. In some embodiments, a cancer is a lymphoma, e.g., Hodgkin lymphoma (HL), non-Hodgkin's lymphoma, lymphocytic lymphoma, or diffuse large B cell lymphoma (DLBCL) (e.g., a relapsed or refractory HL or DLBCL). In some embodiments, a cancer is a myeloma, e.g., multiple myeloma.

[0300] Pharmaceutical composition comprising immune cells as described herein (e.g., stem cells, macrophages, monocytes, or dendritic cells) can be used to enhance or modulate an immune response in a subject. In one embodiment, a pharmaceutical composition described herein enhances, stimulates, or increases an immune response in a subject (e.g., a subject having, or at risk of, a disease or disorder described herein). In certain embodiments, a subject is, or is at risk of being, immunocompromised. For example, a subject is undergoing or has undergone a chemotherapeutic treatment and/or radiation therapy.

[0301] In some embodiments, a subject has, or is at risk of, developing an inflammatory disorder (e.g., a chronic or acute inflammatory disorder). In some embodiments, a subject has, or is at risk, of developing an autoimmune disease or disorder. Exemplary autoimmune diseases that can be treated with methods described herein include, but are not limited to, Alzheimer's disease, asthma (e.g., bronchial asthma), an allergy (e.g., an atopic allergy), Acquired Immunodeficiency Syndrome (AIDS), atherosclerosis, Behcet's disease, celiac, cardiomyopathy, Crohn's disease, cirrhosis, diabetes, diabetic retinopathy, eczema, fibromyalgia, fibromyositis, glomerulonephritis, graft vs. host disease (GVHD), Guillain-Barre syndrome, hemolytic anemia, multiple sclerosis, myasthenia gravis, osteoarthritis, polychondritis, psoriasis, rheumatoid arthritis, sepsis, stroke, vasculitis, ventilator-induced lung injury, transplant rejection, Raynaud's

phenomena, Reiter's syndrome, rheumatic fever, sarcoidosis, scleroderma, Sjogren's syndrome, ulcerative colitis, uveitis, vitiligo, or Wegener's granulomatosis.

[0302] Administration of pharmaceutical compositions described herein may be carried out in any convenient manner (e.g., injection, ingestion, transfusion, inhalation, implantation, or transplantation). In some embodiments, a pharmaceutical compositions described herein is administered by injection or infusion. Pharmaceutical compositions described herein may be administered to a patient transarterially, subcutaneously, intravenously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, or intraperitoneally. In some embodiments, a pharmaceutical composition described herein is administered parenterally (e.g., intravenously, subcutaneously, intraperitoneally, or intramuscularly). In some embodiments, a pharmaceutical composition described herein is administered by intravenous infusion or injection. In some embodiments, a pharmaceutical composition described herein is administered by intramuscular or subcutaneous injection. Pharmaceutical compositions described herein may be injected directly into a site of inflammation, a local disease site, a lymph node, an organ, a tumor, or site of infection in a subject.

[0303] All publications, patent applications, patents, and other references mentioned herein, including GenBank Accession Numbers, are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

[0304] The disclosure is further illustrated by the following examples. An example is provided for illustrative purposes only. It is not to be construed as limiting the scope or content of the disclosure in any way.

EXAMPLES

[0305] The following examples are provided so as to describe to the skilled artisan how to make and use methods and compositions described herein, and are not intended to limit the scope of the present disclosure.

Example 1: Trafficking of Fusion Proteins to Cell Surface of HEK293T Cells

[0306] On Day 0, HEK293T cells were transiently transfected with plasmid DNA using Lipofectamine 3000. On Day 2, the HEK293T cells were evaluated for expression and trafficking of fusion proteins expressed from exemplary constructs of the present disclosure (see **Figure 5A** and **Figure 5B**). Immunostaining for a FLAG-tag at the N-terminus of a fusion protein indicates proper folding and trafficking of the fusion protein to the cell surface, while Western blots were performed to detect full-length fusion protein mass.

[0307] As shown in **Figure 6A**, transfection of HEK293T cells with constructs encoding fusion proteins did not affect the viability of the cells relative to nontransfected cells. As shown in **Figure 6B**, HEK cells were able to express 3 separate fusion proteins (IFN-β and IFNAR1, IL-4 and IL2Rγc and IL-4 and IL13Rα) at the cell surface, as indicated by immunostaining for the FLAG tag. Additionally, as shown in **Figure 7**, there was a correlation between detection of a FLAG tag by an antibody and mCherry expression in the IFNβ-IFNAR1 and IL4-IL13Rα groups. Western blot analyses further confirmed expression of the fusion proteins (see **Figure 8**). By using antibodies that targeted the cytokines (which are small molecular masses), the larger molecular mass that results from direct fusion with the cytokine receptor was detected. Fusion to the cytokine receptor was particularly evident in the case of IFNβ. IFNAR1 is heavily glycosylated, increasing its mass almost 2-fold beyond the predicted mass based off amino acid confirmation, and resulted in a smeared band in the Western blot. By targeting the cytokine IFNβ, the Western blot captured the glycosylated nature of IFNAR1, demonstrating the fusion of these two proteins.

Example 2: Expression of Fusion Proteins in Primary Macrophages

[0308] On Day 0, macrophages were transduced with VPX-Lentivirus comprising a fusion protein (MOI 10). On Day 2, the macrophage media with replaced with fresh media. On

Day 4, flow cytometry (FCM) was performed to analyze surface expression of fusion proteins encoded by exemplary constructs of the present disclosure, with immunostaining for a FLAG-tag at the N-terminus of the fusion protein (see **Figure 9**).

[0309] As shown in **Figure 10A**, transfection of macrophages with constructs encoding fusion proteins reduced viability of the cells relative to nontransfected macrophages. As shown in **Figure 10A** and **Figure 10B**, IL4-based fusion proteins were successfully expressed at the surface of macrophages, while IFN-β-based fusion proteins were not detected at the surface of macrophages. These results, compared to those in Example 1, indicate that macrophages may be more sensitive than HEK293T cells to the design of each fusion protein. Additionally, these results could indicate that surface expression is not necessary for signaling, for example, a functional signaling cascade could occur from the endoplasmic reticulum. Total protein expression can be determined using western blot, while flow cytometry plus cell permeabilization can be used to determine intracellular expression. It is also possible that the IFN-β-based fusion protein was expressed at the cell surface, but was not detectable in the system's signal-to-noise ratio. Finally, the results shown in **Figure 11A** and **Figure 11B** illustrate viability, P2A-mCherry expression, and surface expression of fusion proteins in macrophages transduced with VPX-Lentivirus comprising a fusion protein.

Example 3: Effect of Pro-Inflammatory Fusion Protein on Pro-Inflammatory and Anti-Inflammatory Markers

[0310] On Day 0, macrophages were transduced with VPX-Lentivirus comprising a fusion protein (MOI 10). On Day 3, the macrophage media with replaced with fresh media. On Day 4, flow cytometry (FCM) was performed to analyze pro-inflammatory (i.e., M1) (CD80 and CD86) and anti-inflammatory (i.e. M2) (CD163 and CD206) markers.

[0311] As shown in **Figure 12A** and **Figure 12B**, transduction with a pro-inflammatory fusion protein (IFNβ-IFNAR1) successfully induced a pro-inflammatory macrophage phenotype, with an upregulation in pro-inflammatory markers and a downregulation in anti-inflammatory markers. Transduction with lentivirus alone induces a pro-inflammatory phenotype, so it important to note that the IFNβ-IFNAR1 fusion protein polarized macrophages beyond the effect of lentivirus alone (represented by the mCherry control).

[0312] Although IFNβ-IFNAR1 was not detected at the macrophage surface (see Example 2), results from this M1/M2 panel indicate that surface expression may not be required for fusion protein function.

Example 4: Effect of Cytokine and CAR Co-Expression on Macrophage Viability and CAR Expression

[0313] Macrophages were derived from peripheral blood CD14+ monocytes, which were differentiated using 10 ng/mL GM-CSF for 7 days. Primary human monocyte-derived macrophages were electroporated with 50 μM mRNA (comprising chemical modifications) encoding an anti-HER2 CAR (CAR1) with or without 50 μM mRNA encoding a cytokine. Using flow cytometry, the percent of live cells was quantified after 24 hours (**Figure 13**). Additionally, the percent of CAR+ cells was evaluated using flow cytometry. As shown in **Figure 14**, over 50% of macrophages transfected with CAR, with or without co-transfection with cytokine mRNA, expressed the CAR on their surface within 24 hours.

Example 5: Effect of Cytokine and CAR Co-Expression on Cytokine Expression

[0314] 2 x 10^6 human macrophages were transfected with 50 μM CAR mRNA or with 50 μM CAR mRNA and 50 μM mRNA encoding IFN-γ, IL-10, CCL19, or CXCL12 (see **Figures 15**, **16**, **17** and **18**). Supernatants were collected 24 hours post-electroporation and cytokine levels were evaluated using an MSD instrument. As shown in **Figure 15**, macrophages transfected with CAR mRNA and IFN-γ mRNA (CAR1+IFNg group) secreted high levels of IFN-γ, while transfection with CAR mRNA and mRNA encoding IL-10, CCL19 or CXCL12 did not lead to IFN-γ secretion. Similarly, as shown in **Figure 16**, macrophages co-transfected with CAR and IL-10 mRNAs secreted high levels of IL-10, while macrophages transfected with CAR mRNA and mRNA encoding IFN-γ, CCL19 or CXCL12 did not lead to IL-10 secretion. Also, as shown in **Figure 17**, macrophages transfected with CAR mRNA and CCL19 mRNA secreted high levels of CCL19, while transfection with CAR mRNA and mRNA encoding IFN-γ, IL-10, or CXCL12 did not lead to CCL19 secretion. Finally, as shown in **Figure 18**, macrophages transfected with CAR mRNA and CXCL12 mRNA secreted higher levels of CXCL12 than

transfection with CAR mRNA and mRNA encoding IFN-γ, IL-10, or CCL19. CCL19 and CXCL12 are both chemoattractant chemokines that lead to the recruitment of T cells and other immune cells.

Example 6: Effect of Cytokine and CAR Co-Expression on Macrophage Phenotype

[0315] To evaluate the ability of transfected macrophages to self-polarize to pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, macrophage phenotype was evaluated using flow cytometry 24 hours post-electroporation. As shown in **Figure 19**, macrophages electroporated with CAR mRNA and IFN-γ mRNA (CAR1+IFNg group) demonstrated the highest level of surface expression of human M1 macrophage markers CD80 and CD86. These data demonstrate that co-transfecting a macrophage with CAR mRNA and IFN-γ mRNA allows for polarization to an M1 phenotype. As shown in **Figure 20**, macrophages electroporated with CAR mRNA and IL-10 mRNA (CAR+IL10 group) demonstrated the highest level of surface expression of human M2 macrophage markers CD163 and CD206. These data demonstrate that co-transfecting a macrophage with CAR mRNA and IL-10 mRNA allows for polarization to an M2 phenotype.

EXEMPLARY SEQUENCES

Table 2a – Amino Acid Sequences of Endogenous Proteins (Pro-Inflammatory Cytokines)

Name	Uniprot	Amino Acid Sequence	Notes
IFN-α2	P01563	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFP QEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDET LLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILA VRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQ ESLRSKE **(SEQ ID NO: 1)**	Signal peptide removed
IFN-β	P01574	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNF DIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTGW NETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMS SLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFIN RLTGYLRN **(SEQ ID NO: 2)**	Signal peptide removed
IFN-γ	P01579	QDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKE ESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMN VKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVM AELSPAAKTGKRKRSQMLFRG **(SEQ ID NO: 3)**	Signal peptide removed,

			propeptide removed
TNF-α	P01375	VRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLA NGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTH TISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIY LGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL **(SEQ ID NO: 4)**	Soluble form (TMD removed) - Wang et al 1985
IL-1β	P01584	APVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQ QVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDK PTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQF PNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSS **(SEQ ID NO: 5)**	Propeptide removed for mature form
IL-6	P05231	VPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKE TCNKSNMCESSKEALAENNLNLPKMAEKDGCFQSGFNE ETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTK VLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQ DMTTHLILRSFKEFLQSSLRALRQM **(SEQ ID NO: 6)**	Signal peptide removed
IL-12 subunit p35	p29459	RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEF YPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRET SFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTM NAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQK SSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNAS **(SEQ ID NO: 7)**	Signal peptide removed
IL-12 subunit p40	P29460	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITW TLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSH SLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSG RFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAE RVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHK LKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWE YPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSA TVICRKNASISVRAQDRYYSSSWSEWASVPCS **(SEQ ID NO: 8)**	Signal peptide removed

Table 2b – Amino Acid Sequences of Endogenous Proteins (Anti-Inflammatory Cytokines)

Name	Uniprot	Amino Acid Sequence	Notes
IL-4	P05112	HKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTE KETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLI RFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTI MREKYSKCSS **(SEQ ID NO: 9)**	Signal peptide removed
IL-10	P22301	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQM KDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMP QAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENK SKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTM KIRN **(SEQ ID NO: 10)**	Signal peptide removed

IL-13	P35225	LTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGS MVWSINLTAGMYCAALESLINVSGCSAIEKTQRMLSGFC PHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREG RFN **(SEQ ID NO: 11)**	Signal peptide removed
IL-18	Q14116	YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCR DNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKII SFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSSYE GYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED **(SEQ ID NO: 12)**	Signal peptide removed

Table 3a – Amino Acid Sequences of Endogenous Proteins (Pro-Inflammatory Cytokine Receptors)

Name	Uniprot	Amino Acid Sequence	Notes
IFNAR 1	P17181	KNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFDYQK TGMDNWIKLSGCQNITSTKCNFSSLKLNVYEEIKLRIRAE KENTSSWYEVDSFTPFRKAQIGPPEVHLEAEDKAIVIHISP GTKDSVMWALDGLSFTYSLVIWKNSSGVEERIENIYSRH KIYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVEN ELPPPENIEVSVQNQNYVLKWDYTYANMTFQVQWLHAF LKRNPGNHLYKWKQIPDCENVKTTQCVFPQNVFQKGIYL LRVQASDGNNTSFWSEEIKFDTEIQAFLLPPVFNIRSLSDS FHIYIGAPKQSGNTPVIQDYPLIYEIIFWENTSNAERKIIEK KTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFSDAV CEKTKPGNTSKIWLIVGICIALFALPFVIYAAKVFLRCINY VFFPSLKPSSSIDEYFSEQPLKNLLLSTSEEQIEKCFIIENIST IATVEETNQTDEDHKKYSSQTSQDSGNYSNEDESESKTSE ELQQDFV **(SEQ ID NO: 13)**	Signal peptide removed
IFNAR 2	P48551	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPTHYTL LYTIMSKPEDLKVVKNCANTTRSFCDLTDEWRSTHEAYV TVLEGFSGNTTLFSCSHNFWLAIDMSFEPPEFEIVGFTNHI NVMVKFPSIVEEELQFDLSLVIEEQSEGIVKKHKPEIKGN MSGNFTYIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTL LPPGQESESAESAKIGGIITVFLIALVLTSTIVTLKWIGYICL RNSLPKVLNFHNFLAWPFPNLPPLEAMDMVEVIYINRKK KVWDYNYDDESDSDTEAAPRTSGGGYTMHGLTVRPLGQ ASATSTESQLIDPESEEEPDLPEVDVELPTMPKDSPQQLEL LSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFNVDLNSVF LRVLDDEDSDDLEAPLMLSSHLEEMVDPEDPDNVQSNHL LASGEGTQPTFPSPSSEGLWSEDAPSDQSDTSESDVDLGD GYIMR **(SEQ ID NO: 14)**	Signal peptide removed
IFNGR 1	P15260	EMGTADLGPSSVPTPTNVTIESYNMNPIVYWEYQIMPQVP VFTVEVKNYGVKNSEWIDACINISHHYCNISDHVGDPSNS LWVRVKARVGQKESAYAKSEEFAVCRDGKIGPPKLDIRKE	Signal peptide removed

		EKQIMIDIFHPSVFVNGDEQEVDYDPETTCYIRVYNVYVR MNGSEIQYKILTQKEDDCDEIQCQLAIPVSSLNSQYCVSAE GVLHVWGVTTEKSKEVCITIFNSSIKGSLWIPVVAALLLFL VLSLVFICFYIKKINPLKEKSIILPKSLISVVRSATLETKPESK YVSLITSYQPFSLEKEVVCEEPLSPATVPGMHTEDNPGKV EHTEELSSITEVVTTEENIPDVVPGSHLTPIERESSSPLSSNQ SEPGSIALNSYHSRNCSESDHSRNGFDTDSSCLESHSSLSD SEFPPNNKGEIKTEGQELITVIKAPTSFGYDKPHVLVDLLV DDSGKESLIGYRPTEDSKEFS **(SEQ ID NO: 15)**	
IFNGR 2	P38484	APPDPLSQLPAPQHPKIRLYNAEQVLSWEPVALSNSTRPV VYQVQFKYTDSKWFTADIMSIGVNCTQITATECDFTAASP SAGFPMDFNVTLRLRAELGALHSAWVTMPWFQHYRNVT VGPPENIEVTPGEGSLIIRFSSPFDIADTSTAFFCYYVHYWE KGGIQQVKGPFRSNSISLDNLKPSRVYCLQVQAQLLWNK SNIFRVGHLSNISCYETMADASTELQQVILISVGTFSLLSVL AGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPTQPILE ALDKDSSPKDDVWDSVSIISFPEKEQEDVLQTL **(SEQ ID NO: 16)**	Signal peptide removed
TNFR1	P19438	LVPHLGDREKRDSVCPQGKYIHPQNNSICCTKCHKGTYL YNDCPGPGQDTDCRECESGSFTASENHLRHCLSCSKCRK EMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQCFN CSLCLNGTVHLSCQEKQNTVCTCHAGFFLRENECVSCSN CKKSLECTKLCLPQIENVKGTEDSGTTVLLPLVIFFGLCLL SLLFIGLMYRYQRWKSKLYSIVCGKSTPEKEGELEGTTTK PLAPNPSFSPTPGFTPTLGFSPVPSSTFTSSSTYTPGDCPNF AAPRREVAPPYQGADPILATALASDPIPNPLQKWEDSAHK PQSLDTDDPATLYAVVENVPPLRWKEFVRRLGLSDHEIDR LELQNGRCLREAQYSMLATWRRRTPRREATLELLGRVLR DMDLLGCLEDIEEALCGPAALPPAPSLLR **(SEQ ID NO: 17)**	Signal peptide removed. Membrane bound form
TNFR2	P20333	LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQ HAKVFCTKTSDTVCDSCEDSTYTQLWNWVPECLSCGSR CSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCA PLRKCRPGFGVARPGTETSDVVCKPCAPGTFSNTTSSTDI CRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQ PVSTRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGDFA LPVGLIVGVTALGLLIIGVVNCVIMTQVKKKPLCLQREAK VPHLPADKARGTQGPEQQHLLITAPSSSSSSLESSASALDR RAPTRNQPQAPGVEASGAGEARASTGSSDSSPGGHGTQV NVTCIVNVCSSSDHSSQCSSQASSTMGDTDSSPSESPKDE QVPFSKEECAFRSQLETPETLLGSTEEKPLPLGVPDAGMK PS **(SEQ ID NO: 18)**	Signal peptide removed. Membrane bound form
IL-1R1	P14778	LEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITW YKDDSKTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYYC VVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKLPVAG DGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFS	Signal peptide removed.

		GVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIE FITLEENKPTRPVIVSPANETMEVDLGSQIQLICNVTGQLS DIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLIT VLNISEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQ KHMIGICVTLTVIIVCSVFIYKIFKIDIVLWYRDSCYDFLPI KASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEK QCGYKLFIYGRDDYVGEDIVEVINENVKKSRRLIIILVRET SGFSWLGGSSEEQIAMYNALVQDGIKVVLLELEKIQDYE KMPESIKFIKQKHGAIRWSGDFTQGPQSAKTRFWKNVRY HMPVQRRSPSSKHQLLSPATKEKLQREAHVPLG **(SEQ ID NO: 19)**	Membrane bound form
IL-1R3	Q9NPH3	SERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYST AHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVL WFRPTLLNDTGNYTCMLRNTTYCSKVAFPLEVVQKDSCF NSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWY MGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPE NGRTFHLTRTLTVKVVGSPKNAVPPVIHSPNDHVVYEKEP GEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTI NESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKG EVAKAAKVKQKVPAPRYTVELACGFGATVLLVVILIVVY HVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAE EEEFVLLTLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSF IQKSRRLLVVLSPNYVLQGTQALLELKAGLENMASRGNI NVILVQYKAVKETKVKELKRAKTVLTVIKWKGEKSKYP QGRFWKQLQVAMPVKKSPRRSSSDEQGLSYSSLKNV **(SEQ ID NO: 20)**	Signal peptide removed
IL-6Rα	P08887	LAPRRCPAQEVARGVLTSLPGDSVTLTCPGVEPEDNATVH WVLRKPAAGSHPSRWAGMGRRLLLRSVQLHDSGNYSCY RAGRPAGTVHLLVDVPPEEPQLSCFRKSPLSNVVCEWGP RSTPSLTTKAVLLVRKFQNSPAEDFQEPCQYSQESQKFSC QLAVPEGDSSFYIVSMCVASSVGSKFSKTQTFQGCGILQP DPPANITVTAVARNPRWLSVTWQDPHSWNSSFYRLRFEL RYRAERSKTFTTWMVKDLQHHCVIHDAWSGLRHVVQL RAQEEFGQGEWSEWSPEAMGTPWTESRSPPAENEVSTP MQALTTNKDDDNILFRDSANATSLPVQDSSSVPLPTFLVA GGSLAFGTLLCIAIVLRFKKTWKLRALKEGKTSMHPPYS LGQLVPERPRPTPVLVPLISPPVSPSSLGSDNTSSHNRPDA RDPRSPYDISNTDYFFPR **(SEQ ID NO: 21)**	Signal peptide removed. Membrane bound form
gp130	P40189	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVN ANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTC NILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRC EWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCT VDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVK PNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRT KDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMK EDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQ	Signal peptide removed

		GYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYT VNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDF QATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWC VLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVT PVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVL EWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEY TLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQG EIEAIVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPD PSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEI EANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSS SRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQV FSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFK QNCSQHESSPDISHFERSKQVSSVNEEDFVRLKQQISDHIS QSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEA ATDEGMPKSYLPQTVRQGGYMPQ **(SEQ ID NO: 22)**	
IL-12-Rβ1	P42701	CRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECS WQYEGPTAGVSHFLRCCLSSGRCCYFAAGSATRLQFSDQ AGVSVLYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEP PLGDIKVSKLAGQLRMEWETPDNQVGAEVQFRHRTPSSP WKLGDCGPQDDDTESCLCPLEMNVAQEFQLRRRQLGSQ GSSWSKWSSPVCVPPENPPQPQVRFSVEQLGQDGRRRLT LKEQPTQLELPEGCQGLAPGTEVTYRLQLHMLSCPCKAK ATRTLHLGKMPYLSGAAYNVAVISSNQFGPGLNQTWHIPA DTHTEPVALNISVGTNGTTMYWPARAQSMTYCIEWQPV GQDGGLATCSLTAPQDPDPAGMATYSWSRESGAMGQEK CYYITIFASAHPEKLTLWSTVLSTYHFGGNASAAGTPHHV SVKNHSLDSVSVDWAPSLLSTCPGVLKEYVVRCRDEDSK QVSEHPVQPTETQVTLSGLRAGVAYTVQVRADTAWLRG VWSQPQRFSIEVQVSDWLIFFASLGSFLSILLVGVLGYLGL NRAARHLCPPLPTPCASSAIEFPGGKETWQWINPVDFQEE ASLQEALVVEMSWDKGERTEPLEKTELPEGAPELALDTE LSLEDGDRCKAKM **(SEQ ID NO: 23)**	Signal peptide removed
IL-12-Rβ2	Q99665	KIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFHYS RRNKLILYKFDRRINFHHGHSLNSQVTGLPLGTTLFVCKL ACINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQGTVACT WERGRDTHLYTEYTLQLSGPKNLTWQKQCKDIYCDYLD FGINLTPESPESNFTAKVTAVNSLGSSSSLPSTFTFLDIVRPL PPWDIRIKFQKASVSRCTLYWRDEGLVLLNRLRYRPSNSR LWNMVNVTKAKGRHDLLDLKPFTEYEFQISSKLHLYKGS WSDWSESLRAQTPEEEPTGMLDVWYMKRHIDYSRQQIS LFWKNLSVSEARGKILHYQVTLQELTGGKAMTQNITGHT SWTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGL LAPRQVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWR ELHPGGDTQVPLNWLRSRPYNVSALISENIKSYICYEIRV YALSGDQGGCSSILGNSKHKAPLSGPHINAITEEKGSILIS WNSIPVQEQMGCLLHYRIYWKERDSNSQPQLCEIPYRVS	Signal peptide removed

		QNSHPINSLQPRVTYVLWMTALTAAGESSHGNEREFCLQ GKANWMAFVAPSICIAIIMVGIFSTHYFQQKVFVLLAALR PQWCSREIPDPANSTCAKKYPIAEEKTQLPLDRLLIDWPT PEDPEPLVISEVLHQVTPVFRHPPCSNWPQREKGIQGHQA SEKDMMHSASSPPPPRALQAESRQLVDLYKVLESRGSDP KPENPACPWTVLPAGDLPTHDGYLPSNIDDLPSHEAPLAD SLEELEPQHISLSVFPSSSLHPLTFSCGDKLTLDQLKMRCD SLML **(SEQ ID NO: 24)**	

Table 3b – Amino Acid Sequences of Endogenous Proteins (Anti-Inflammatory Cytokine Receptors)

Name	Uniprot	Amino Acid Sequence	Notes
IL-4Rα	P24394	MKVLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLYQL VFLLSEAHTCIPENNGGAGCVCHLLMDDVVSADNYTLD LWAGQQLLWKGSFKPSEHVKPRAPGNLTVHTNVSDTLLL TWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYL EPSLRIAASTLKSGISYRARVRAWAQCYNTTWSEWSPSTK WHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKE WWDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPH WKNCLTKLLPCFLEHNMKRDEDPHKAAKEMPFQGSGKS AWCPVEISKTVLWPESISVVRCVELFEAPVECEEEEEVEE EKGSFCASPESSRDDFQEGREGIVARLTESLFLDLLGEENG GFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPW GKEQPLHLEPSPPASPTQSPDNLTCTETPLVIAGNPAYRSFS NSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTT VPQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVH AVEQGGTQASAVVGLGPPGEAGYKAFSSLLASSAVSPEK CGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGLDR EPPRSPQSSHLPSSSPEHLGLEPGEKVEDMPKPPLPQEQAT DPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQTPVM ASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLEASLCPASL APSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTY MRVS **(SEQ ID NO: 25)**	Signal peptide removed. Membrane bound form
IL-2Rγc	P31785	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCF VFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQ KCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRR QATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFL NHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQK RYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENPF LFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLE DLVTEYHGNFSAWSGVSKGLAESLQPDYSERLCLVSEIPP KGGALGEGPGASPCNQHSPYWAPPCYTLKPET **(SEQ ID NO: 26)**	Signal peptide removed

IL-13Rα1	P78552	GGGGAAPTETQPPVTNLSVSVENLCTVIWTWNPPEGASS NCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGS QCSTNESEKPSILVEKCISPPEGDPESAVTELQCIWHNLSY MKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREG QYFGCSFDLTKVKDSSFEQHSVQIMVKDNAGKIKPSFNIV PLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFY EVEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFM VPGVLPDTLNTVRIRVKTNKLCYEDDKLWSNWSQEMSIG KKRNSTLYITMLLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDP GKIFKEMFGDQNDDTLHWKKYDIYEKQTKEETDSVVLIE NLKKASQ **(SEQ ID NO: 27)**	Signal peptide removed
IL-10R1	Q13651	HGTELPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALL RYGIESWNSISNCSQTLSYDLTAVTLDLYHSNGYRARVRA VDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHNGFILG KIQLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTH KKVKHENFSLLTSGEVGEFCVQVKPSVASRSNKGMWSK EECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYVR RRKKLPSVLLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLK VSPELKNLDLHGSTDSGFGSTKPSLQTEEPQFLLPDPHPQ ADRTLGNREPPVLGDSCSSGSSNSTDSGICLQEPSLSPSTG PTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSAL GHHSPPEPEVPGEEDPAAVAFQGYLRQTRCAEEKATKTG CLEEESPLTDGLGPKFGRCLVDEAGLHPPALAKGYLKQD PLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDW SFAHDLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 28)**	Signal peptide removed
IL-10R2	Q08334	MVPPPENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLS YRIFQDKCMNTTLTECDFSSLSKYGDHTLRVRAEFADEHS DWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLAPKIEN EYETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDF EVLRNLEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQTT HDETVPSWMVAVILMASVFMVCLALLGCFALLWCVYKK TKYAFSPRNSLPQHLKEFLGHPHHNTLLFFSFPLSDENDV FDKLSVIAEDSESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 29)**	Signal peptide removed
IL-18Rα	Q13478	AESCTSRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYK SSGSQEHVELNPRSSSRIALHDCVLEFWPVELNDTGSYFF QMKNYTQKWKLNVIRRNKHSCFTERQVTSKIVEVKKFF QITCENSYYQTLVNSTSLYKNCKKLLLENNKNPTIKKNAE FEDQGYYSCVHFLHHNGKLFNITKTFNITIVEDRSNIVPVL LGPKLNHVAVELGKNVRLNCSALLNEEDVIYWMFGEEN GSDPNIHEEKEMRIMTPEGKWHASKVLRIENIGESNLNVL YNCTVASTGGTDTKSFILVRKADMADIPGHVFTRGMIIAV LILVAVVCLVTVCVIYRVDLVLFYRHLTRRDETLTDGKTY DAFVSYLKECRPENGEEHTFAVEILPRVLEKHFGYKLCIFE RDVVPGGAVVDEIHSLIEKSRRLIIVLSKSYMSNEVRYELE	Signal peptide removed

		SGLHEALVERKIKIILIEFTPVTDFTFLPQSLKLLKSHRVLK WKADKSLSYNSRFWKNLLYLMPAKTVKPGRDEPEVLPV LSES **(SEQ ID NO: 30)**	
IL-18Rβ	O95256	FNISGCSTKKLLWTYSTRSEEEFVLFCDLPEPQKSHFCHR NRLSPKQVPEHLPFMGSNDLSDVQWYQQPSNGDPLEDIR KSYPHIIQDKCTLHFLTPGVNNSGSYICRPKMIKSPYDVAC CVKMILEVKPQTNASCEYSASHKQDLLLGSTGSISCPSLS CQSDAQSPAVTWYKNGKLLSVERSNRIVVDEVYDYHQG TYVCDYTQSDTVSSWTVRAVVQVRTIVGDTKLKPDILDP VEDTLEVELGKPLTISCKARFGFERVFNPVIKWYIKDSDL EWEVSVPEAKSIKSTLKDEIIERNIILEKVTQRDLRRKFVC FVQNSIGNTTQSVQLKEKRGVVLLYILLGTIGTLVAVLAA SALLYRHWIEIVLLYRTYQSKDQTLGDKKDFDAFVSYAK WSSFPSEATSSLSEEHLALSLFPDVLENKYGYSLCLLERD VAPGGVYAEDIVSIIKRSRRGIFILSPNYVNGPSIFELQAAV NLALDDQTLKLILIKFCYFQEPESLPHLVKKALRVLPTVT WRGLKSVPPNSRFWAKMRYHMPVKNSQGFTWNQLRITS RIFQWKGLSRTETTGRSSQPKEW **(SEQ ID NO: 31)**	Signal peptide removed

Table 4a – Codon Optimized DNA Sequences of Endogenous Proteins (Pro-Inflammatory Cytokines)

Name	Uniprot	Codon Optimized Sequence	Notes
IFN-α2	P01563	Tgcgaccttccacagacccattccctcggctctcgaagaactctgatgttgctggcccaga tgcggaagatttctcttttctcatgtctgaaagacaggcacgactttggttttccccaggagg agttcggaaaccagttccagaaagcggaaaccattcctgtgctgcacgaaatgatccaac aaattttcaacctgttttcaactaaagatagctccgctgcatgggacgagacactcctcgata agttttatacagagctttaccagcagttaaatgatctggaagcttgtgtcatccaaggggtcg gcgtaaccgagacgcccctgatgaaggaggatagcatactggcagtgcggaagtacttc cagaggatcaccctctatctaaaggaaaaaaagtacagtccgtgcgcctgggaagtggtt agagccgaaatcatgcgtagcttttccttatctacaaatttgcaggagtcgttgcgcagtaaa gag **(SEQ ID NO: 32)**	Signal peptide removed
IFN-β	P01574	Atgagttataatttactcggatttctacagcggtctagcaacttccaatgtcagaagctgctg tggcaactcaacggcaggctggagtactgcctcaaagatagaatgaactttgatattcccg aagaaatcaagcagcttcagcagttccagaaagaggacgccgcactaaccatatacgag atgctgcagaacattttcgctatattcagacaggactcgtcctctactggatggaatgagac catcgtcgagaatttgctggccaatgtgtatcatcaaattaaccacctcaagacggtgcttga agaaaagttggaaaaagaggacttcactagaggcaaactgatgtcatcccttcacctcaaa cgctactatgggaggatcctgcactacttaaaggcgaaggagtatagccattgcgcttgga caatcgttcgcgtagagattctgcggaatttttactttatcaatcgtttgacaggttacctgcga aac **(SEQ ID NO: 33)**	Signal peptide removed
IFN-γ	P01579	Caggatccctacgtgaaggaagcagaaaatctcaaaaagtatttcaatgcgggccatagc gatgtggccgataacggcaccctgtttctggggattcttaagaattggaaagaggagtctg ataggaagattatgcagtcccagatcgtgagcttctatttcaagctgttcaaaaacttcaaag acgaccagtcgatccaaaaatctgttgagacaataaaagaggacatgaatgtgaagtttttt	Signal peptide removed,

		aattcaaacaaaaagaagcgcgacgattttgagaaattaacgaactactccgtcaccgact tgaacgtacaacgaaaggctattcacgaactaatccaggtcatggctgaactgagtcctgc cgccaagactggtaagcgtaaacggagtcagatgctctttagagga **(SEQ ID NO: 34)**	propeptide removed
TNF-α	P01375	Gtgcgatcttcaagccggacaccctcagacaagccagtggcacacgtggtagcgaacc cacaagctgaggggcagctccagtggctcaatcggcgtgccaacgccctgttagccaat ggggtcgagcttagggacaaccaacttgtggtaccctcggaaggattatacttgatttacag tcaggtgctgttcaaaggacagggctgcccttccacacatgttctgctcactcacacgatct cccgcattgcagtgtcttatcagaccaaggtcaacttgctaagcgctatcaaaagtccatgt cagagagagaccccggagggtgctgaggctaagccttggtacgaacctatttatctgggc ggagtctttcaactggaaaaaggtgatagactgagcgcagagatcaataggcccgattac ctggacttcgccgaatccggccaggtttattttgggataatcgccctc **(SEQ ID NO: 35)**	Soluble form (TMD removed) - Wang et al 1985
IL-1β	P01584	Gcgcctgtcagaagcctcaactgcacgctgagggactcacagcaaaagagcctggtcat gagtggcccctacgagctgaaagcactccaccttcaggggcaggacatggaacaacag gtggttttctccatgtctttcgtacagggagaggagtctaacgataagatccccgtggctttg ggcttaaaagagaaaaacctgtatctgagctgtgtgctaaaggacgataagcccacacttc agctcgagtccgttgatccaaaaaattatccaaagaagaaaatggaaaagcggtttgtgttt aacaagattgagattaataacaaattggaattcgaatcagcccagttccctaattggtacatc agtacctctcaagccgaaaatatgccggtgtttctgggagggaccaagggtggccaggat ataacagacttcactatgcagtttgtctcgtcc **(SEQ ID NO: 36)**	Propeptide removed for mature form
IL-6	P05231	Gtgccgcccggggaagatagcaaggatgtggctgctcctcacaggcagccactgacaa gcagcgagagaatcgacaagcaaataaggtatattcttgatggaatcagcgcgctgcgaa aggagacatgtaacaagtcgaatatgtgcgagtcttccaaagaagcacttgctgaaaataa tctgaacctcccaaaaatggccgagaaagacggctgctttcagtccggttttaacgaggag acttgtttagtaaagattataacgggcttgttggaattcgaagtctacctagaatacctccaaa atagattcgagagtagtgaggaacaggcccgcgctgttcagatgtcaacaaaagtgttgat ccaattcctgcagaaaaaagccaagaacttagatgcaatcaccacacctgaccccactac caatgcctctctgctcaccaagctgcaagcccagaaccagtggctgcaggacatgactac ccatctaattctgcggtcttttaaggagttcctccagtcatccctgcgtgcacttcggcagatg **(SEQ ID NO: 37)**	Signal peptide removed
IL-12 subunit p35	p29459	Cgaaatctgccagtggctacccccgacccgggcatgtttccctgcctccatcatagccag aatctgctcagagcggtcagcaacatgctacagaaggcccgccagaccttagagttttacc cttgcacctctgaggaaatcgatcacgaagacatcaccaaagataagactagcaccgttg aagcctgtctcccattggaacttacaaaaaatgaatcttgtctgaattccagagagacatctttt tatcactaatggaagttgcctcgccagtcggaaaacttccttcatgatggccctgtgtctgag ttcaatctacgaggatcttaagatgtatcaagtggaattcaaaacgatgaacgcaaaactgtt gatggatcctaagaggcagatatttttggatcagaacatgttagctgtgatcgacgagctga tgcaagcactcaacttcaactcagagacagtcccccagaagtcctccctggaggagcctg acttctacaagacgaaaattaagctatgcattctgcttcacgcattcaggatacgggccgta acaattgaccgtgtgatgagctatctgaacgcttcg **(SEQ ID NO: 38)**	Signal peptide removed
IL-12 subunit p40	P29460	Atctgggagctcaaaaaggatgtttatgtggtcgaacttgactggtacccggacgcacca ggggagatggtggtgttgacctgcgacacccccgaagaggacgggattacatggacttt ggaccagtccagtgaagtcctgggctcgggaaagaccctgactatccaggtgaaggagt tcggagatgctggacaatatacatgccacaagggcggggaagttttgagccattccctcct gctgctgcataaaaaagaggatggtatttggagcactgatattctgaaagaccagaaggaa	Signal peptide removed

		cccaagaacaaaactttctgcggtgtgaggccaagaattacagtggaagattcacctgttg gtggttaaccacaatctctaccgatcttacctttccgtcaaatcaagtcgcggcagcagcg atccacagggcgtgacgtgcggcgctgccacactaagcgcggagagagtgcggggtg acaacaaggaatacgagtactccgttgagtgtcaagaagactctgcatgccctgccgcag aggaatcattaccgatcgaagtaatggtggatgctgttcacaaactgaagtatgaaaactac acttcttcatttttcataagggacattatcaagcctgatcctccaaagaacctccaacttaaac cactcaagaatagccgtcaggtagaggtgtcctgggagtaccccgatacctggtcaacgc cccactcatatttctccctgacgttctgtgtgcaggtgcaggggaaatccaagagggagaa gaaagacagggtctttacagataagacatctgccactgtcatctgcagaaaaaatgcctcta tatccgtgcgagcccaggaccgctactattctagtagctggagcgagtgggctagtgtacc ttgttcg **(SEQ ID NO: 39)**	

Table 4b – Codon Optimized DNA Sequences of Endogenous Proteins (Anti-Inflammatory Cytokines)

Name	Uniprot	Codon Optimized Sequence	Notes
IL-4	P05112	Cacaagtgtgatattacactccaagaaataatcaagaccctgaacagcctaaccgagcag aaaactctctgtacggaattgaccgttaccgatatcttcgcagctagtaagaatacaactga aaaagagacgttttgtcgtgccgccacagtcctgaggcagttttattcacatcacgagaaag acacccggtgccttggggcaactgcccaacagtttcatcgccacaaacagctgatcagatt cttgaagcggctggacaggaatctctggggattagctggcctgaattcttgccccgtgaag gaggcgaaccagagcactctggagaacttcctggaacgacttaagacaattatgagaga gaagtactccaaatgctcctct **(SEQ ID NO: 40)**	Signal peptide removed
IL-10	P22301	Tcacccggacagggtactcaatctgaaaatagttgcacccattttccaggaaatctgccta acatgctgagggacttacgcgatgcattttcgcgtgtaaaaacattctttcagatgaaagatc aactggataacctgttgctaaaagagagcctgcttgaggatttcaagggctatctgggctgt caggcgctctccgaaatgattcaattctacctcgaagaggtgatgccccaggccgagaac caggacccagacatcaaggcccacgtgaattctctgggggagaatctgaaaacgctcag attgcgactcagacggtgccacaggtttttaccttgtgaaaacaagagcaaagccgttgag caggtcaagaacgcttttaataagcttcaggaaaaagggatctataaggcaatgtccgagtt cgacatattcattaattacattgaggcttacatgaccatgaagatccggaac **(SEQ ID NO: 41)**	Signal peptide removed
IL-13	P35225	Ttaacatgtctgggcgggttcgcctcacctggaccagttccccccttcaaccgctctcagag aactgattgaggagctcgtcaatatcacccagaaccaaaaagccccactctgcaatggaa gtatggtgtggtctattaacttgactgccggcatgtactgtgccgcactggagtctttgatca acgtgtccgggtgcagtgcaatcgaaaagacgcagcggatgctgagcggcttttgcccc cacaaggtgagcgctggtcagttttccagccttcacgtgcgagatacaaagatagaagtag cgcagttcgtcaaggacctgctgctgcatcttaaaaaactatttcgcgagggtaggttcaat **(SEQ ID NO: 42)**	Signal peptide removed
IL-18	Q14116	Tattttggcaaactcgaaagtaagctgagcgtgattcggaatcttaacgatcaggtgttattc atcgatcaaggcaacagaccactctttgaagatatgacagattcagactgtagggataatg cccctaggaccatctttattataagcatgtataaggactctcagccccgcggtatggcagta acgattagcgttaagtgcgagaagatttctacactttcatgcgaaaacaaaatcatctccttc aaagagatgaaccctcccgataatatcaaagataccaagtcggacataattttctttcagag atccgtcccaggacacgacaataagatgcaattcgaatccagcagttacgagggatacttt	Signal peptide removed

		ctggcttgtgagaaggaacgtgacttgttcaaactgatcctgaagaaagaggacgagcta ggggaccgatctatcatgttcactgtgcagaacgaggac **(SEQ ID NO: 43)**	

Table 5a – Codon Optimized DNA Sequences of Endogenous Proteins (Pro-Inflammatory Cytokine Receptors)

Name	Uniprot	Codon Optimized Sequence	Notes
IFNAR1	P17181	aagaacctgaaatccccacagaaagtcgaggtggacatcatcgatgacaatttcatcttaag atggaaccgtagcgatgagtccgtcggaaatgtcacattttcttttgattatcagaagaccgg gatggacaactggattaagctgtccggttgccagaacataaccagtaccaagtgtaacttca gcagcctcaaactcaatgtatatgaggaaatcaagctgaggatccgggccgagaaggaaa acacaagctcctggtatgaagttgattcatttactccatttcgaaaagcgcaaataggacccc cggaagttcacctcgaggctgaagataaagcaattgtaatacacatatcgcctggcaccaa ggactctgtgatgtgggctttagatgggctgtcattcacgtacagcctggtgatctggaagaa cagttctggggtggaggagagaatagaaaacatttatagtcgccacaaaatctacaaattgt cacccgaaacaacctattgcctgaaggtcaaggcggcactattgacgtcctggaagatcgg cgtgtactcaccagtgcattgtataaagacaacagtggaaaacgagcttccccgccggag aatattgaggtttccgtgcagaatcagaattatgtgttgaagtgggactacacatatgccaata tgaccttccaggttcaatggcttcatgcatttctgaaaagaaaccctggtaaccacctttacaa atggaagcagattcctgactgcgagaatgtcaagaccacacagtgcgtgtttcctcaaaacg ttttccagaaaggcatctatctgctacgggtccaggcttccgatggcaataatacctcattttg gagcgaggaaattaaattcgacactgaaatccaagccttcctactccctcccgtatttaacat caggagtctgtctgatagcttccatatttacatcggtgctcccaagcagtctggaaacactcc cgtgatccaggattacccctcatctacgagatcattttctgggaaaacacctctaacgccga acggaagattatagagaagaaaactgacgtcactgtgcctaacctgaaaccattaactgtct attgcgtcaaagctagggcccacaccatggatgaaaaactgaacaagtctagcgtgttcag cgacgcagtttgtgagaaaacgaagccaggaaatacttctaagatttggcttatcgtgggca tttgtatcgctctgttcgcactgccctttgtaatctacgccgccaaggtttttctccgctgtattaa ttatgtgtttttcccatccctgaagccatcatcgtcgattgacgagtacttctctgagcaacctct taaaaacctgttgttgtccaccagtgaagagcagattgagaaatgcttcattatcgaaaatattt caacaatcgccacagtggaggagacgaatcagaccgacgaggaccataagaagtacag cagtcagacatctcaggattccgggaattacagcaatgaagatgaaagtgaatccaaaact agcgaggagctccaacaggactttgtg **(SEQ ID NO: 44)**	Signal peptide removed
IFNAR2	P48551	atcagctacgactcccccgattacaccgacgagtcctgtacctttaaaatctccctacgtaact tcaggtccattctctcctgggaactgaaaaaccatagcattgtgccgactcactatacactgct gtataccataatgtctaaacccgaggatctgaaggtggtgaagaactgtgcgaacaccaca agatccttctgcgacctgacagatgagtggcgatctacccatgaagcctacgtcacggtcct cgagggcttcagcggtaataccacacttttcagctgctcacataacttttggttggccatcgat atgtcctttgaaccacccgagttcgagattgtcggtttcacaaaccacatcaatgtcatggtga aatttccttctattgtcgaggaagaactccagtttgatttgagcctcgtgattgaggagcagtc agagggaatcgtgaagaagcataagcccgaaataaagggaaatatgagtgggaacttcac ttacataatcgacaagctcatccccaacacgaattattgtgtgtcagtgtatctcgagcactcg	Signal peptide removed

		gatgagcaagccgtgatcaagtctccacttaagtgcactctcctgccgccaggccaggagt cagagagcgctgaatcggctaagataggcgggatcattaccgtcttcctcatcgcactggtg ttgacttctactattgttaccctgaagtggatcggatacatctgcttgcgcaactctctgccaaa agttctaaactttcacaattttctggcctggcccttccccaatcttcctcctctggaggccatgg acatggttgaggttatctatataaatcggaaaaaaaaagtctgggactacaattacgatgacg aaagtgactcagacacggaggccgcaccaaggacctctggaggggggctatactatgcac ggccttaccgtgagacctttaggacaggcatctgctacaagcactgaaagccagctgattg acccagagagcgaggaagagcctgatctaccagaagtggatgtagagctgccgacaatg cctaaggactccccccaacagctcgaactgttgagcggcccttgtgaaaggcgcaaaagt cccttgcaagatccgttccctgaagaagactatagcagtaccgaaggatccggcggtcgga ttacattcaacgtggatttaaatagtgtatttttacgggttctggacgatgaggacagtgatgat ctggaggcgccccttatgctgtcctcccatctggaggagatggtagaccccgaagatccag ataacgtgcagtctaatcaccttctggcttccggggaaggtactcagccaacctttcctagtc cttcttcagagggcttatggtcagaagacgcaccaagcgatcagtcagacacaagtgagag cgacgtagacctcgggggacgggtacattatgaga **(SEQ ID NO: 45)**	
IFNGR1	P15260	gaaatggggactgccgacttgggacctagcagtgtccccactcccaccaacgtgaccatc gagtcttataatatgaatcctattgtttattgggaatatcagatcatgcctcaggttccagtgttc actgttgaagtgaaaaattacggagtgaagaactcagagtggatagacgcttgcataaacat atctcaccattactgcaatatttccgaccacgtgggcgaccccagcaacagtttgtgggtca gagtgaaagctcgcgtgggccagaaggagagtgcttatgccaaaagcgaagaattcgcc gtttgtagagatggcaagatcgggccccccaaattagacattcgcaaagaagaaaaacaa attatgatcgatatcttccatccctctgtcttcgtcaacggcgacgaacaggaggtagattatg atccagagacaacgtgttacatcagggtatacaacgtttacgtgaggatgaatgggtcaga gatccagtataagatcctcactcaaaaggaggacgactgtgacgaaattcagtgtcaactc gccatcccagtgtcttcgctgaatagccagtactgcgtgtctgccgagggtgtgcttcacgtt tggggagtcacaactgaaaagtccaaagaagtttgtattaccatttttaacagctctatcaag ggctccctgtggataccagtggtggcggcactgctgctgttccttgtactcagcctggtcttc atctgcttctatattaagaagatcaaccctctgaaggagaagagcatcatactacccaagtcg cttatctcagtcgtgcggtccgccaccctagaaactaagcccgaatcaaaatatgtatccctg atcacaagctaccagccattttcattagagaaagaagtcgtgtgcgaggagcctctgtcccc agcaactgtgccaggtatgcatacggaggacaatccgggtaaagtagagcacaccgagg agctgtccagcattacagaggtcgtcaccacagaggagaacatacccgatgtggtgcctg gaagtcatctcacacctattgagcgtgaatctagcagtcccttgtcttctaatcagagtgaacc ggggagtattgcattaaactcctaccactcccggaattgcagcgaaagcgaccactcgaga aatgggtttgataccgatagttcttgtctggaatcccactcatcactgagcgattctgagtttcc gccaaacaacaagggcgaaattaaaacggagggacaagagctcatcaccgtcatcaagg ctccaaccagttttggttacgacaagcctcatgttttggtggatctgcttgtggatgactcagg caaggagtccctcattggataccgacctacagaggattccaaagagtttagc **(SEQ ID NO: 46)**	Signal peptide removed
IFNGR2	P38484	Gccccccctgatcctctctcacagctacccgccccacagcatcccaagataagactgtaca atgccgagcaggtgcttagctgggagcccgtggcactatcaaacagtacgagacccgtgg tgtaccaggtacagttcaagtacacagacagcaagtggtttaccgctgacattatgagcatt ggagtcaattgcactcagatcaccgcaaccgagtgtgactttacagcagcttcaccctccgc cggattccctatggacttcaacgtcactctgcggcttcgtgcagaactgggcgctcttcattc cgcctgggtgacaatgccttggttccagcactatcggaacgtcaccgtagggcccccgaa aatatcgaagtaacccctggagaaggttcgctgataataaggttcagctctccgtttgacatt	Signal peptide removed

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IL-12-Rβ2	Q99665	aaaattgatgcgtgcaaacgcggcgatgtgaccgtgaaaccgagccatgtgattctgctgg gcagcaccgtgaacattacctgcagcctgaaaccgcgccagggctgctttcattatagccg ccgcaacaaactgattctgtataaatttgatcgccgcattaactttcatcatggccatagcctg aacagccaggtgaccggcctgccgctgggcaccaccctgtttgtgtgcaaactggcgtgc attaacagcgatgaaattcagatttgcggcgcggaaatttttgtgggcgtggcgccggaaca gccgcagaacctgagctgcattcagaaaggcgaacagggcaccgtggcgtgcacctggg aacgcggccgcgataccatctgtataccgaatataccctgcagctgagcggcccgaaaa acctgacctggcagaaacagtgcaaagatatttattgcgattatctggattttggcattaacct gaccccggaaagcccggaaagcaactttaccgcgaaagtgaccgcggtgaacagcctgg gcagcagcagcagcctgccgagcacctttacctttctggatattgtgcgcccgctgccgcc gtgggatattcgcattaaatttcagaaagcgagcgtgagccgctgcaccctgtattggcgcg atgaaggcctggtgctgctgaaccgcctgcgctatcgcccgagcaacagccgcctgtgga acatggtgaacgtgaccaaagcgaaaggccgccatgatctgctggatctgaaaccgtttac cgaatatgaatttcagattagcagcaaactgcatctgtataaaggcagctggagcgattgga gcgaaagcctgcgcgcgcagaccccggaagaagaaccgaccggcatgctggatgtgtg gtatatgaaacgccatattgattatagccgccagcagattagcctgttttggaaaaacctgag cgtgagcgaagcgcgcggcaaaattctgcattatcaggtgaccctgcaggaactgaccgg cggcaaagcgatgacccagaacattaccggccataccagctggaccaccgtgattccgcg caccggcaactgggcggtggcggtgagcgcggcgaacagcaaaggcagcagcctgcc gacccgcattaacattatgaacctgtgcgaagcgggcctgctggcgccgcgccaggtgag cgcgaacagcgaaggcatggataacattctggtgacctggcagccgccgcgcaaagatc cgagcgcggtgcaggaatatgtggtggaatggcgcgaactgcatccgggcggcgatacc caggtgccgctgaactggctgcgcagccgcccgtataacgtgagcgcgctgattagcgaa aacattaaaagctatatttgctatgaaattcgcgtgtatgcgctgagcggcgatcagggcgg ctgcagcagcattctgggcaacagcaaacataaagcgccgctgagcggcccgcatattaa	Signal peptide removed

		cgcgattaccgaagaaaaaggcagcattctgattagctggaacagcattccggtgcaggaa cagatgggctgcctgctgcattatcgcatttattggaaagaacgcgatagcaacagccagc cgcagctgtgcgaaattccgtatcgcgtgagccagaacagccatccgattaacagcctgca gccgcgcgtgacctatgtgctgtggatgaccgcgctgaccgcggcgggcgaaagcagcc atggcaacgaacgcgaattttgcctgcagggcaaagcgaactggatggcgtttgtggcgc cgagcatttgcattgcgattattatggtgggcatttttagcacccattattttcagcagaaagtgt ttgtgctgctggcggcgctgcgcccgcagtggtgcagccgcgaaattccggatccggcga acagcacctgcgcgaaaaaatatccgattgcggaagaaaaaacccagctgccgctggatc gcctgctgattgattggccgacccccggaagatccggaaccgctggtgattagcgaagtgct gcatcaggtgaccccggtgtttcgccatccgccgtgcagcaactggccgcagcgcgaaaa aggcattcagggccatcaggcgagcgaaaaagatatgatgcatagcgcgagcagcccgc cgccgccgcgcgcgctgcaggcggaaagccgccagctggtggatctgtataaagtgctg gaaagccgcggcagcgatccgaaaccggaaaacccggcgtgcccgtggaccgtgctgc cggcgggcgatctgccgacccatgatggctatctgccgagcaacattgatgatctgccgag ccatgaagcgccgctggcggatagcctggaagaactggaaccgcagcatattagcctgag cgtgtttccgagcagcagcctgcatccgctgacctttagctgcggcgataaactgaccctgg atcagctgaaaatgcgctgcgatagcctgatgctg **(SEQ ID NO: 55)**	

Table 5b – Codon Optimized DNA Sequences of Endogenous Proteins (Anti-Inflammatory Cytokine Receptors)

Name	Uniprot	Codon Optimized Sequence	Notes
IL-4Rα	P24394	atgaaagtgctgcaggaaccgacctgcgtgagcgattatatgagcattagcacctgcgaat ggaaaatgaacggcccgaccaactgcagcaccgaactgcgcctgctgtatcagctggtgtt tctgctgagcgaagcgcatacctgcattccggaaaacaacggcggcgcgggctgcgtgtg ccatctgctgatggatgatgtggtgagcgcggataactataccctggatctgtgggcgggc cagcagctgctgtggaaaggcagctttaaaccgagcgaacatgtgaaaccgcgcgcgcc gggcaacctgaccgtgcataccaacgtgagcgataccctgctgctgacctggagcaaccc gtatccgccggataactatctgtataaccatctgacctatgcggtgaacatttggagcgaaaa cgatccggcggattttcgcatttataacgtgacctatctggaaccgagcctgcgcattgcgg cgagcaccctgaaaagcggcattagctatcgcgcgcgcgtgcgcgcgtgggcgcagtgc tataacaccacctggagcgaatggagcccgagcaccaaatggcataacagctatcgcgaa ccgtttgaacagcatctgctgctgggcgtgagcgtgagctgcattgtgattctggcggtgtg cctgctgtgctatgtgagcattaccaaaattaaaaaagaatggtgggatcagattccgaacc cggcgcgcagccgcctggtggcgattattattcaggatgcgcagggcagccagtgggaa aaacgcagccgcggccaggaaccggcgaaatgcccgcattggaaaaactgcctgacca aactgctgccgtgctttctggaacataacatgaaacgcgatgaagatccgcataaagcggc gaaagaaatgccgtttcagggcagcggcaaaagcgcgtggtgcccggtggaaattagca aaaccgtgctgtggccggaaagcattagcgtggtgcgctgcgtggaactgtttgaagcgcc ggtggaatgcgaagaagaagaagaagtggaagaagaaaaaggcagcttttgcgcgagc ccggaaagcagccgcgatgattttcaggaaggccgcgaaggcattgtggcgcgcctgac cgaaagcctgtttctggatctgctgggcgaagaaaacggcggcttttgccagcaggatatg ggcgaaagctgcctgctgccgccgagcggcagcaccagcgcgcatatgccgtgggatg aatttccgagcgcgggcccgaaagaagcgccgccgtggggcaaagaacagccgctgca tctggaaccgagcccgccggcgagcccgacccagagcccggataacctgacctgcacc gaaaccccgctggtgattgcgggcaacccggcgtatcgcagctttagcaacagcctgagc	Signal peptide removed. Membrane bound form

		cagagcccgtgcccgcgcgaactgggcccggatccgctgctggcgcgccatctggaaga agtggaaccggaaatgccgtgcgtgccgcagctgagcgaaccgaccaccgtgccgcag ccggaaccggaaacctgggaacagattctgcgccgcaacgtgctgcagcatggcgcggc ggcggcgccggtgagcgcgccgaccagcggctatcaggaatttgtgcatgcggtggaac agggcggcacccaggcgagcgcggtggtgggcctgggcccgccgggcgaagcgggc tataaagcgtttagcagcctgctggcgagcagcgcggtgagcccggaaaaatgcggctttt ggcgcgagcagcggcgaagaaggctataaaccgtttcaggatctgattccgggctgcccg ggcgatccggcgccggtgccggtgccgctgtttacctttggcctggatcgcgaaccgccg cgcagcccgcagagcagccatctgccgagcagcagcccggaacatctgggcctggaac cgggcgaaaaagtggaagatatgccgaaaccgccgctgccgcaggaacaggcgaccga tccgctggtggatagcctgggcagcggcattgtgtatagcgcgctgacctgccatctgtgc ggccatctgaaacagtgccatggccaggaagatggcggccagaccccggtgatggcga gcccgtgctgcggctgctgctgcggcgatcgcagcagcccgccgaccaccccgctgcgc gcgccggatccgagcccgggcggcgtgccgctggaagcgagcctgtgcccggcgagc ctggcgccgagcggcattagcgaaaaaagcaaaagcagcagcagctttcatccggcgcc gggcaacgcgcagagcagcagccagaccccgaaaattgtgaactttgtgagcgtgggcc cgacctatatgcgcgtgagc **(SEQ ID NO: 56)**	
IL-2Rγc	P31785	Ctgaacacaacaattctcacccctaacggcaacgaagacactaccgcagatttttttcctcac tactatgcccactgattccctttccgtgtcgaccttgccgctgccagaagtgcagtgcttcgtc tttaatgttgagtatatgaattgtacatggaattctagcagcgaaccgcagccaaccaatttga cattgcactactggtataaaaactcagataacgacaaagtgcagaagtgttcccactacttatt tagcgaggaaataacctctgggtgccagctgcagaagaaggagatccatctgtaccagac cttcgtcgtgcagctccaggatccacgggaaccacgccggcaagctacccaaatgctaaa gctgcaaaatctcgttatcccatgggcacctgagaatttgacacttcataagctgtcggaatc ccagctggagctcaattggaacaaccgtttcctcaaccattgtctggagcacctggtgcagt acagaaccgactgggaccatagttggacggagcagagtgtcgattatagacacaaattctc actaccctcagtggacgggcagaagaggtacacatttagagtaaggagtcggttcaatccc ctgtgcgggtccgcccaacactggagtgagtggtctcatcctattcactggggcagcaaca cgtccaaggagaaccctttcttgtttgctctggaagctgttgtgatttcagtaggctctatggg attaatcatcagcctcctgtgtgtctatttttggctggagcgaacaatgcccaggatccccact ctcaaaaatctggaagaccttgtgacggagtatcacggcaacttcagcgcgtggtctggcgt ctctaaaggtcttgccgagagcctgcagcctgattacagtgagcgcttatgcctggtgagcg agataccacctaaaggaggagcccttggtgaaggaccgggggcatccccctgtaatcaac actcaccatactgggcccccccctgctataccctaaagcctgaaact **(SEQ ID NO: 57)**	Signal peptide removed
IL-13Rα1	P78552	ggcggcggcggcgcggcgccgaccgaaacccagccgccggtgaccaacctgagcgtg agcgtggaaaacctgtgcaccgtgatttggacctggaacccgccggaaggcgcgagcag caactgcagcctgtggtattttagccattttggcgataaacaggataaaaaaattgcgccgga aacccgccgcagcattgaagtgccgctgaacgaacgcatttgcctgcaggtgggcagcca gtgcagcaccaacgaaagcgaaaaaccgagcattctggtggaaaaatgcattagcccgcc ggaaggcgatccggaaagcgcggtgaccgaactgcagtgcatttggcataacctgagcta tatgaaatgcagctggctgccgggccgcaacaccagcccggataccaactataccctgtat tattggcatcgcagcctggaaaaaattcatcagtgcgaaaacatttttcgcgaaggccagtat tttggctgcagctttgatctgaccaaagtgaaagatagcagctttgaacagcatagcgtgca gattatggtgaaagataacgcgggcaaaattaaaccgagctttaacattgtgccgctgacca gccgcgtgaaaccggatccgccgcatattaaaaacctgagctttcataacgatgatctgtat	Signal peptide removed

		gtgcagtgggaaaacccgcagaactttattagccgctgcctgttttatgaagtggaagtgaa caacagccagaccgaaacccataacgtgttttatgtgcaggaagcgaaatgcgaaaaccc ggaatttgaacgcaacgtggaaaacaccagctgctttatggtgccgggcgtgctgccggat accctgaacaccgtgcgcattcgcgtgaaaaccaacaaactgtgctatgaagatgataaact gtggagcaactggagccaggaaatgagcattggcaaaaaacgcaacagcaccctgtatat taccatgctgctgattgtgccggtgattgtggcgggcgcgattattgtgctgctgctgtatctg aaacgcctgaaaattattatttttccgccgattccggatccgggcaaaatttttaaagaaatgtt tggcgatcagaacgatgataccctgcattggaaaaaatatgatatttatgaaaaacagacca aagaagaaaccgatagcgtggtgctgattgaaaacctgaaaaaagcgagccag **(SEQ ID NO: 58)**	
IL-10R1	Q13651	catgggaccgagctccccagtcctccttctgtttggttcgaagccgaattctttcaccatattct gcactggactcctatcccaaatcaatcagaatcaacatgttacgaggtggcactgctgaggt acggaatcgagtcttggaatagcatttcaaactgtagccaaaccctgtcttacgatcttaccg ctgtgacgctggacctgtatcatagcaacggctaccgtgccagggttagggcagttgatgg cagcagacactccaattggacagttacgaatacccgattcagtgtcgacgaggtgactttaa ctgtcgggagtgttaaccttgaaattcacaacgggttcatattgggaaagatccagctccccc ggccaaaaatggccccagccaacgacacatacgagagtatattttctcattttagagagtatg agatcgcaatccgcaaggtgcctgggaatttcacatttactcataagaaggtaaaacacgag aacttctccttgctcacctccggcgaagtgggggagttctgcgtgcaggtgaagccctcggt ggcttcacgctccaataaaggcatgtggagcaaagaagaatgtatttctctgactcggcagt actttaccgtgactaacgtaatcatatttttgccttcgtgctcctgctgtctggtgccctggcct attgcctggcgcttcaactttatgtgcggaggaggaagaagctgccgtccgtgctgttgttta agaaaccgtctcccttcatttttatcagccagcgcccctcacccgaaacacaggatactattc acccccttgacgaagaagccttccttaaagtgtccccgagctaaaaaacctcgacctgca cgggtccaccgatagcgggtttggtagcaccaaaccatccttgcaaaccgaggagcccca gttcttgctccctgatccacacccacaggctgacagaacgttgggaaacagagagccccca gtcctgggggattcctgttcgtcagggtctagtaatagtaccgatagcgggatttgcctgcag gagccgagcctgtcaccctcaaccggtccgacctgggagcagcaagtaggatctaactcc cgcgggcaggatgactccggcatagacctcgtacagaattcggaaggccgggcgggtga cacacagggcggctccgctctgggccaccattccccaccagagcccgaggtccctggcg aggaggaccctgcagccgtcgcttttcaaggctatctgcgtcagacacgatgtgctgaaga gaaagctactaagacgggatgtcttgaagaggaatctccgcttacagacggattgggacca aagttcggcagatgcctagtggatgaggcgggactacatcctcccgcattagcaaagggct acctgaagcaggatccactagaaatgacactggcctcatctggcgcccctacaggacagt ggaaccagccaaccgaagagtggtccttgctcgctttaagctcttgcagtgacctgggtatc tcagattggagttttgcacacgacctcgcccctctgggttgcgtcgccgctcctggtggactc ttaggaagtttcaatagcgatctcgtcactctgcctctcatcagtagcttacagagcagcgaa **(SEQ ID NO: 59)**	Signal peptide removed
IL-10R2	Q08334	Atggtaccaccacctgaaaatgtgaggatgaactctgtgaattttaagaacattctccagtgg gaaagtcccgcttttgctaaggggaacctgaccttcacagcccaatacttatcctaccgaatc ttccaagacaagtgcatgaataccactttaactgaatgcgacttctcaagcctgtctaagtatg gcgatcatacactgcgggttcgtgccgagtttgccgacgagcactctgactgggtgaatata accttctgccccgtcgatgatactataattgggccaccaggtatgcaagttgaagtgttggca gattcgctgcacatgaggtttctcgcccccaaaatcgagaacgagtacgagacctggacga tgaagaatgtctacaactcttggacatataatgttcagtattggaaaaacggaaccgacgag aagtttcagatcactccgcagtatgatttcgaagtcctgagaaacctcgagccttggacaact	Signal peptide removed

		tactgtgtccaagtgcgcggctttctccctgaccggaacaaggcaggagagtggtcagaac cggtgtgtgagcagaccacccacgacgagacagtacccagctggatggtagctgtgatcc ttatggcctccgtgttcatggtttgtctagctttgttgggctgttttgcccttctatggtgcgtctat aaaaagaccaaatacgcgttttcacctagaaacagccttccacagcacctcaaggagttcct ggggcatcctcatcacaatacactgctgttcttctccttccccctgagtgacgaaaacgatgt gtttgataaactgtccgtgattgcagaagacagtgagtccggcaaacagaatccaggagat agttgcagcctgggtacgcctcccggacagggcccccagagc **(SEQ ID NO: 60)**	
IL-18Rα	Q13478	gccgagagctgcactagccggccccatataactgtggtcgaaggggagccattctatctga aacattgttcctgctcccttgcccatgaaattgaaaccacaaccaagagctggtacaaatcta gtgggtctcaagagcacgtcgagttgaacccaagatcatctagtaggatcgccctgcatga ctgcgttctagagttttggccggtggaattaaatgacaccggatcttacttcttccagatgaag aattacacccagaaatggaagctgaacgtgatacgacgcaacaagcactcatgcttcacag aacgtcaggtgacctcgaaaatcgtggaagtgaaaaagttctttcagattacatgcgagaac agttactatcaaacgctagtgaatagcacgagcctgtacaaaaactgtaagaaacttctgctg gagaacaataaaaaccctactatcaaaaaaaatgcagaattcgaggatcagggctattaca gttgtgtgcattttctccaccacaatggtaagctattcaatatcaccaagacgttcaacatcacc attgtggaggatcgctccaacatagtacctgtgttattgggtcctaaacttaaccacgtggca gtggagctggggaaaaacgtgagactcaattgctcagccttgctgaacgaagaggatgtta tttattggatgtttggggaagaaaatggaagtgacccgaacattcacgaagagaaggagat gcgaatcatgacaccagaggggaaatggcacgcgagtaaggtcctcagaattgaaaatatt ggcgaatcaaatctcaacgtcctctataactgtaccgtagcatccacaggcggcactgatac taagtcctttatccttgtgcgtaaggccgatatggctgacatccccggccacgtattcacacg gggaatgatcattgctgttctgatcctggtggcagtagtgtgtttggttactgtatgtgttatcta ccgcgtggacttagttctgttttataggcacctgacccgaagagacgaaacccttacagatg gcaagacttatgacgcgttcgtgtcgtatcttaaagaatgccggcccgagaatggagagga gcacacgtttgctgtcgaaattctccccagagtcctggagaagcattttggttacaagctgtg catcttcgaaagagacgtcgtgcccggtggcgccgtggtcgacgagatacattccctgatc gagaagtcccgcaggttgatcatagtcctctcaaagtcttacatgagcaatgaggtgcggta cgaactcgagagcggactgcatgaggctttagtcgagaggaagattaagattattttgatcg agtttacacctgtgactgactttaccttcctccctcagtcactgaaactccttaagtctcacagg gtactgaagtggaaagctgataaatccctctcttataatagccggttttggaagaacctattgt acctgatgccagccaaaacagtcaagcctggacgcgatgagcccgaagttctgccagttct gagcgagtcc **(SEQ ID NO: 61)**	Signal peptide removed
IL-18Rβ	O95256	tttaatatctctggatgcagtacgaagaaattgctctggacatactctactaggagcgaggaa gagttcgtgcttttctgcgatttaccagaaccacagaaatcccatttttgtcacagaaatcgtct ttctcctaagcaggttcccgaacacctgcccttcatgggctccaacgaccttagtgacgttca atggtaccagcaaccaagcaatggcgaccctctggaagacatacgcaagagttaccccca tattatccaggataaatgcacgctacatttcctgaccccaggcgtcaacaacagtggatcttat atatgtaggcctaagatgatcaaatccccctacgacgtggcttgttgcgtcaagatgattctc gaggtgaagccccagaccaatgcctcatgtgagtactccgcctctcacaaacaggaccttc tgctggggtcgaccggcagtataagctgcccatcgctctcttgtcagagtgatgcgcagag ccctgctgtgacatggtacaaaaacggaaagctactgtcagtggagcgctcaaaccgtatt gtagtagacgaagtctacgactatcaccaaggcacctacgtgtgcgattatacacagtctga tacggtctccagttggactgtgcgggccgtggtgcaggtacggaccatcgtgggggacac aaaactgaagcccgacatccttgatccagttgaggacaccctggaggtggagctcgggaa	Signal peptide removed

		gcccctgactatctcctgtaaagcaagatttggcttcgagcgagtatttaaccctgttatcaag tggtatattaaagatagcgatctcgagtgggaggtatcagtgcctgaagccaaatccatcaa atcaactctgaaggatgaaatcattgagcgaaatattattcttgagaaggttacccagcgcga tctccgccgcaaatttgtctgcttcgtgcaaaacagcataggcaatactactcagagcgtgca gctgaaagagaagcgtggtgtcgtcttgttgtacatcctgctcggaacaattggtacactcgt agccgtgttggccgcctcagccctgctctacaggcattggattgaaatcgtgttgctttacag gacatatcagagcaaggaccagactctgggcgacaaaaaggatttcgatgcattcgttagc tatgctaaatggtcttcatttcctagcgaagctacatcctccctgagcgaggaacacttagcct tatcactgtttccagatgtgttagaaaataaatatggctatagcctgtgtttgctggagcgcga cgttgcaccaggggggggtgtatgctgaagacatcgtcagcatcatcaagcggtccaggag gggaatatttatattaagccctaactacgtcaacggtccatcgattttcgaactgcaggctgca gtgaacttggcgctcgatgaccagacgctcaagctgattctcatcaagttctgctactttcaag agcccgagtctcttcctcacctagtcaagaaggcgctgagagtcctgccgaccgtgacatg gcgaggactaaagtctgtgccgccgaattccagattctgggcaaagatgcggtatcatatgc ccgttaaaaattcccaaggttttacttggaaccagctgcggattaccagtcggatcttccagtg gaaggggctgtctagaaccgagaccaccggaagatccagtcaacccaaagaatgg **(SEQ ID NO: 62)**	

Table 6 – Amino Acid Sequences of Engineered Proteins (Cytokines)

Name	Amino Acid Sequence	Notes
scIFN-γ	QDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKI MQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKR DDFEKLTNYSVTDLNVQRKAIHELIQVMAELGANVSGEFVKEAEN LKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFK LFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSV TDLNVQRKAIHELIQVMAELSPAAKTGKRKRSQMLFRG **(SEQ ID NO: 63)**	Single chain; Randal et al 2000
cpIL-1β (89/88)	NYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVF LGGTKGGQDITDFTMQFVSSggggsggggsggggsAPVRSLNCTLRDSQ QKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDKIPV ALGLKEKNLYLSCVLKDDKPTLQLESVDPK **(SEQ ID NO: 64)**	Circular permutation
scIL-12	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSS EVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGI WSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSV KSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPA AEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKN SRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTD KTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGSTSGSGKPG SGEGSTKGRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTL EFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITN GSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKR QIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCIL LHAFRIRAVTIDRVMSYLNAS **(SEQ ID NO: 65)**	Single chain; p40-linker-p35, Lee et al 2001

cpIL-4 (38-37)	NTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRF LKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKC SSggnggHKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASK **(SEQ ID NO: 66)**	Circular permutation; Kreitman et al 1994
mIL-10	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLD NLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKA HVNSLGENLKTLRLRLRRCHRFLPCENGGGSGGKSKAVEQVKNA FNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN **(SEQ ID NO: 67)**	Monomeric form; Josephson et al 2000
cpIL-10 (58/57)	GYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTL RLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFI NYIEAYMTMKIRNggggsggggsggggsSPGQGTQSENSCTHFPGNLPN MLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFK **(SEQ ID NO: 68)**	Circular permutation
tdIL-10	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLD NLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKA HVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQE KGIYKAMSEFDIFINYIEAYMTMKIRNggggsggggsggggsSPGQGTQS ENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLL EDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGEN LKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSE FDIFINYIEAYMTMKIRN **(SEQ ID NO: 69)**	Tandem-dimer
cpIL-13 (75/74)	VSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFNggggsLTC LGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTA GMYCAALESLINVSGCSAIEKTQRMLSGFCPHK **(SEQ ID NO: 70)**	Circular permutation

Table 7 – Codon Optimized DNA Sequences of Engineered Proteins (Cytokines)

Name	Codon Optimized Sequence	Notes
scIFN-γ	Caggatccctacgtgaaagaagccgagaacttaaagaaatatttcaacgcaggccattcagacgtcgct gataatggaacacttttttgggcattctgaaaaattggaaggaagaatcggaccgaaaaattatgcagag ccagatagtatccttttatttcaagttatttaaaaacttcaaagacgatcagtctatccaaaaaagtgtggaga ctatcaaggaggacatgaatgtgaagttcttcaacagcaataaaaagaaacgggatgactttgaaaagct caccaattactcagtcactgatctgaacgtgcagagaaaggcgattcatgagctaatccaagtgatggct gagctcggagccaacgtgagcggagagtttgtgaaggaagccgagaatctgaagaagtatttcaacgct ggtcactctgacgtggcagataacggcacgctgttcctggggatcctgaagaattggaaagaagagtcc gacaggaagattatgcaatcccagatcgtcagtttctactttaagcttttcaagaatttcaaagacgatcaga gtatccagaagtctgtcgagaccataaaagaagacatgaatgtaaagttttttaattcaaacaaaaagaag cgtgacgatttcgaaaaactcaccaactactccgttacagatctgaacgttcagagaaaagccattcacga gttgatccaagttatggccgagctctctcctgcagctaagacaggtaagaggaaacggagccagatgct gtttcgcggg **(SEQ ID NO: 71)**	Single chain; Randal et al 2000
cpIL-1β (89/88)	Aactaccccaaaaaaaagatggagaagcggtttgtttttaacaagattgagatcaacaataagctggaatt cgagtctgcgcagttcccaaactggtatattagcacatcgcaagcagaaaatatgcccgtgttcctcggc ggaaccaaaggcgggcaggatatcacagactttacgatgcagttcgtgtcatctggtggtggtggaagc ggcgggggaggcagtgggggaggcgggtccgccccagtgaggtccctgaactgtaccttaagagact cacagcaaaagtccctggtcatgtctggcccctacgaactgaaagcccttcacctgcaggggcaagata	Circular permutation

	tggagcagcaggtggttttcagcatgagttttgtacagggcgaagagagtaatgacaagatacctgtggc tctaggactcaaggaaaagaatttgtatctcagctgcgtcctgaaggacgataaacctactcttcagttgga gtccgtcgatccgaaa **(SEQ ID NO: 72)**	
scIL-12	atctgggagctcaaaaaggatgtttatgtggtcgaacttgactggtacccggacgcaccaggggagatg gtggtgttgacctgcgacacccccgaagaggacgggattacatggactttggaccagtccagtgaagtc ctgggctcgggaaagaccctgactatccaggtgaaggagttcggagatgctggacaatatacatgccac aagggcggggaagttttgagccattccctcctgctgctgcataaaaaagaggatggtatttggagcactg atattctgaaagaccagaaggaacccaagaacaaaacttttctgcggtgtgaggccaagaattacagtgg aagattcacctgttggtggttaaccacaatctctaccgatcttacctttccgtcaaatcaagtcgcggcagc agcgatccacagggcgtgacgtgcggcgctgccacactaagcgcggagagagtgcggggtgacaac aaggaatacgagtactccgttgagtgtcaagaagactctgcatgccctgccgcagaggaatcattaccga tcgaagtaatggtggatgctgttcacaaactgaagtatgaaaactacacttcttcatttttcataagggacatt atcaagcctgatcctccaaagaacctccaacttaaaccactcaagaatagccgtcaggtagaggtgtcct gggagtaccccgatacctggtcaacgccccactcatatttctccctgacgttctgtgtgcaggtgcaggg gaaatccaagagggagaagaaagacagggtctttacagataagacatctgccactgtcatctgcagaaa aaatgcctctatatccgtgcgagcccaggaccgctactattctagtagctggagcgagtgggctagtgta ccttgttcgggctcaaccagcggatccgggaaacccggttctggcgaggggagtacaaagggacgaa atctgccagtggctacccccgacccgggcatgtttccctgcctccatcatagccagaatctgctcagagc ggtcagcaacatgctacagaaggcccgccagaccttagagttttacccttgcacctctgaggaaatcgat cacgaagacatcaccaaagataagactagcaccgttgaagcctgtctcccattggaacttacaaaaaatg aatcttgtctgaattccagagagacatcttttatcactaatggaagttgcctcgccagtcggaaaacttccttc atgatggccctgtgtctgagttcaatctacgaggatcttaagatgtatcaagtggaattcaaaacgatgaac gcaaaactgttgatggatcctaagaggcagatatttttggatcagaacatgttagctgtgatcgacgagctg atgcaagcactcaacttcaactcagagacagtcccccagaagtcctccctggaggagcctgacttctaca agacgaaaattaagctatgcattctgcttcacgcattcaggatacgggccgtaacaattgaccgtgtgatg agctatctgaacgcttcg **(SEQ ID NO: 73)**	Single Chain; p40-linker-p35, Lee et al 2001
cpIL-4 (38-37)	Aatacgactgagaaagagacctttgtagggctgccacagtcctgcggcagttctatagtcaccatgaga aagacaccagatgtctgggggcaaccgctcagcaattccatagacacaagcagttaatccgatttctgaa gcggcttgatcgtaacttgtggggactagccggcctgaactcatgccccgtgaaagaagcgaatcagtc cactcttgagaacttcctcgaaaggctcaagacaattatgcgcgaaaagtacagcaagtgcagctctggc ggaaacggtgggcacaagtgtgatattacgctccaagaaatcatcaagactctgaactccctgaccgag cagaaaacactttgcactgagttgacagtgaccgacatattcgccgctagcaaa **(SEQ ID NO: 74)**	Circular permutation; Kreitman et al 1994
mIL-10	Tcgcctggccagggaacgcagagtgaaaatagctgtacccactttcccggcaacctaccaaatatgctc agagatctgcgggatgcattctcccgggtgaagacatttttccaaatgaaggatcagttggacaaccttct gttgaaggagtcactcttagaggacttcaagggatacctggggtgccaagccctgtctgagatgattcagt tctacctcgaagaggtaatgccacaggccgaaaaccaggaccctgatataaaagctcatgtcaatagttt aggcgagaatctgaaaactctcaggctgcgtctgcgaagatgccaccgctttctgccctgtgagaacgg gggagggtctggtggcaaaagcaaagctgtggagcaagttaaaaatgcattcaacaaacttcaggaga agggtatttataaggcgatgtccgaatttgacatctttattaattacatcgaagcctatatgaccatgaagatc aggaac **(SEQ ID NO: 75)**	Monomeric form; Josephson et al 2000
cpIL-10 (58/57)	Ggttacttgggctgtcaggctctgagtgaaatgattcagttctatcttgaagaggttatgcctcaggcgga gaaccaagacccagacatcaaggcccatgtgaactctctcggggagaatctgaaaacactgcgactgc ggttaagacgttgccacaggttcctaccctgcgaaaataaaagcaaggccgtcgagcaagtgaaaaac gcattcaataaactccaggaaaagggaatttacaaggccatgtccgagtttgatatctttataaactatattg aggcttacatgaccatgaagatccgcaatggtggtggtggaagcggcgggggaggcagtgggggag	Circular permutation

	gcgggtcctcccctggccagggaactcagtcagaaaatagctgcacacactttccagggaatctcccca acatgttgagagatctgagggacgccttctctcgggtgaaaacctttttccaaatgaaagaccagctggac aacctccttctgaaggagagtttactagaggatttcaag **(SEQ ID NO: 76)**	
tdIL-10	Tctccgggacagggaacccagagcgaaaactcctgcactcattttcctggcaacctccccaatatgctg cgagacttgcgcgacgcattctcaagggtgaagacgttcttccagatgaaggatcaactggacaacttatt gctgaaagaatctctgctcgaggatttcaaaggatacctgggatgtcaggcactgagcgagatgatccaa ttttacctggaggaggtcatgcctcaggctgagaatcaggatcctgacatcaaggcccacgtgaacagtc ttggagagaatcttaagacccttaggctgagacttagacggtgtcaccgctttctgccctgcgaaaataaat caaaagcggtggaacaggttaagaacgcttttaataagctgcaggaaaagggcatttataaagctatgag tgaatttgacattttcattaactatatcgaggcctatatgacaatgaaaattaggaacgggggaggcggga gcgggggcggcggctcaggcggtgggggtcctctccaggtcaaggaacacaatctgagaactcctg cacacacttccccggcaatctaccaaacatgctcagagatctcagggacgcgttcagtcgagtgaaaact ttcttccagatgaaggatcagctggacaatctactgctgaaagaaagcttgcttgaggattttaaaggctat ctgggttgtcaggccttatcggagatgatccagttttacttggaggaagttatgcctcaggcagaaaacca agaccccgatatcaaggctcatgtgaattccctcggtgaaaacctaaagaccttacgcctgcgtctcaga cggtgtcatcggtttttgccatgcgagaataagtccaaagccgtagagcaggtcaagaatgccttcaataa gctccaggagaaggggatatacaaagcaatgagcgaatttgacattttcatcaactacatagaggcctac atgaccatgaagatccggaac **(SEQ ID NO: 77)**	Tandem-dimer
cpIL-13 (75/74)	Gtgagcgcgggccagtttagcagcctgcatgtgcgcgataccaaaattgaagtggcgcagtttgtgaaa gatctgctgctgcatctgaaaaaactgtttcgcgaaggccgctttaacggaggaggtggatctctgacctg cctgggcggctttgcgagcccgggcccggtgccgccgagcaccgcgctgcgcgaactgattgaagaa ctggtgaacattacccagaaccagaaagcgccgctgtgcaacggcagcatggtgtggagcattaacctg accgcgggcatgtattgcgcggcgctggaaagcctgattaacgtgagcggctgcagcgcgattgaaaa aacccagcgcatgctgagcggcttttgcccgcataaa **(SEQ ID NO: 78)**	Circular permutation

Table 8 – Sequences of Linkers and Signal Peptide

Name	Amino Acid Sequence	Codon Optimized
(G4S)3 linker	GGGGSGGGGSGGGGS **(SEQ ID NO: 171)**	Ggtggtggtggaagcggcgggggaggcagtgggggaggcgg gtcc **(SEQ ID NO: 79)**
Whitlow linker	GSTSGSGKPGSGEGSTKG **(SEQ ID NO: 172)**	Ggctcaaccagcggatccgggaaacccggttctggcgagggg agtacaaaggga **(SEQ ID NO: 80)**
Linker 26	SGGGSGGGGSGGGGSGGGGSGGG SLQ **(SEQ ID NO: 173)**	Tctggaggcggaagcgggggtggcggcagcggcggtggagg atcaggtggcgggggggtccgggggcggaagtctgcag **(SEQ ID NO: 81)**
CD8a signal peptide	MALPVTALLLPLALLLHAARP **(SEQ ID NO: 174)**	ATGGCCTTGCCTGTGACCGCATTACTGCT TCCACTCGCCCTGCTCCTGCACGCTGCG AGACCC **(SEQ ID NO: 82)**

Table 9 – Amino Acid Sequences of Full Fusion Proteins (all constructs designed with representative signal peptide (CD8a) and flexible linker (linker 26))

Cytokine	Receptor	Amino Acid Sequence
IFN-α2	IFNAR1	MALPVTALLLPLALLLHAARPCDLPQTHSLGSRRTLMLLAQMRKIS LFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSS AAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAV RKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKES GGGSGGGGSGGGGSGGGGSGGGSLQKNLKSPQKVEVDIIDDNFILR WNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNITSTKCNFSSLK LNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEAEDK AIVIHISPGTKDSVMWALDGLSFTYSLVIWKNSSGVEERIENIYSRHK IYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVENELPPPENIE VSVQNQNYVLKWDYTYANMTFQVQWLHAFLKRNPGNHLYKWKQ IPDCENVKTTQCVFPQNVFQKGIYLLRVQASDGNNTSFWSEEIKFDT EIQAFLLPPVFNIRSLSDSFHIYIGAPKQSGNTPVIQDYPLIYEIIFWEN TSNAERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFS DAVCEKTKPGNTSKIWLIVGICIALFALPFVIYAAKVFLRCINYVFFPS LKPSSSIDEYFSEQPLKNLLLSTSEEQIEKCFIIENISTIATVEETNQTD EDHKKYSSQTSQDSGNYSNEDESESKTSEELQQDFV **(SEQ ID NO: 83)**
IFN-α2	IFNAR2	MALPVTALLLPLALLLHAARPCDLPQTHSLGSRRTLMLLAQMRKIS LFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSS AAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAV RKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKES GGGSGGGGSGGGGSGGGGSGGGSLQISYDSPDYTDESCTFKISLRN FRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNCANTTRSFCD LTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPEFEI VGFTNHINVMVKFPSIVEEELQFDLSLVIEEQSEGIVKKHKPEIKGN MSGNFTYIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTLLPPGQES ESAESAKIGGIITVFLIALVLTSTIVTLKWIGYICLRNSLPKVLNFHNF LAWPFPNLPPLEAMDMVEVIYINRKKKVWDYNYDDESDSDTEAAP RTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEEPDLPEVDVEL PTMPKDSPQQLELLSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFN VDLNSVFLRVLDDEDSDDLEAPLMLSSHLEEMVDPEDPDNVQSNH LLASGEGTQPTFPSPSSEGLWSEDAPSDQSDTSESDVDLGDGYIMR **(SEQ ID NO: 84)**
IFN-β	IFNAR1	MALPVTALLLPLALLLHAARPMSYNLLGFLQRSSNFQCQKLLWQL NGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFR QDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLM SSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYL RNSGGGSGGGGSGGGGSGGGGSGGGSLQKNLKSPQKVEVDIIDDN FILRWNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNITSTKCNFS SLKLNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEA EDKAIVIHISPGTKDSVMWALDGLSFTYSLVIWKNSSGVEERIENIYS RHKIYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVENELPPP

		ENIEVSVQNQNYVLKWDYTYANMTFQVQWLHAFLKRNPGNHLYK WKQIPDCENVKTTQCVFPQNVFQKGIYLLRVQASDGNNTSFWSEEI KFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQSGNTPVIQDYPLIYEII FWENTSNAERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNK SSVFSDAVCEKTKPGNTSKIWLIVGICIALFALPFVIYAAKVFLRCINY VFFPSLKPSSSIDEYFSEQPLKNLLLSTSEEQIEKCFIIENISTIATVEET NQTDEDHKKYSSQTSQDSGNYSNEDESESKTSEELQQDFV **(SEQ ID NO: 85)**
IFN-β	IFNAR2	MALPVTALLLPLALLLHAARPMSYNLLGFLQRSSNFQCQKLLWQL NGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFR QDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLM SSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYL RNSGGGSGGGGSGGGGSGGGGSGGGSLQISYDSPDYTDESCTFKIS LRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNCANTTRS FCDLTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPE FEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQSEGIVKKHKPEIKG NMSGNFTYIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTLLPPGQE SESAESAKIGGIITVFLIALVLTSTIVTLKWIGYICLRNSLPKVLNFHN FLAWPFPNLPPLEAMDMVEVIYINRKKKVWDYNYDDESDSDTEAA PRTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEEPDLPEVDVE LPTMPKDSPQQLELLSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFN VDLNSVFLRVLDDEDSDDLEAPLMLSSHLEEMVDPEDPDNVQSNH LLASGEGTQPTFPSPSSEGLWSEDAPSDQSDTSESDVDLGDGYIMR **(SEQ ID NO: 86)**
IFN-γ	IFNGR1	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVAD NGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVE TIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQV MAELSPAAKTGKRKRSQMLFRGSGGGSGGGGSGGGGSGGGGSGG GSLQEMGTADLGPSSVPTPTNVTIESYNMNPIVYWEYQIMPQVPVF TVEVKNYGVKNSEWIDACINISHHYCNISDHVGDPSNSLWVRVKA RVGQKESAYAKSEEFAVCRDGKIGPPKLDIRKEEKQIMIDIFHPSVFV NGDEQEVDYDPETTCYIRVYNVYVRMNGSEIQYKILTQKEDDCDEI QCQLAIPVSSLNSQYCVSAEGVLHVWGVTTEKSKEVCITIFNSSIKG SLWIPVVAALLLFLVLSLVFICFYIKKINPLKEKSIILPKSLISVVRSAT LETKPESKYVSLITSYQPFSLEKEVVCEEPLSPATVPGMHTEDNPGK VEHTEELSSITEVVTTEENIPDVVPGSHLTPIERESSSPLSSNQSEPGSI ALNSYHSRNCSESDHSRNGFDTDSSCLESHSSLSDSEFPPNNKGEIK TEGQELITVIKAPTSFGYDKPHVLVDLLVDDSGKESLIGYRPTEDSK EFS **(SEQ ID NO: 87)**
IFN-γ	IFNGR2	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVAD NGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVE TIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQV MAELSPAAKTGKRKRSQMLFRGSGGGSGGGGSGGGGSGGGGSGG GSLQAPPDPLSQLPAPQHPKIRLYNAEQVLSWEPVALSNSTRPVVYQ VQFKYTDSKWFTADIMSIGVNCTQITATECDFTAASPSAGFPMDFN VTLRLRAELGALHSAWVTMPWFQHYRNVTVGPPENIEVTPGEGSLI

		IRFSSPFDIADTSTAFFCYYVHYWEKGGIQQVKGPFRSNSISLDNLKP SRVYCLQVQAQLLWNKSNIFRVGHLSNISCYETMADASTELQQVILI SVGTFSLLSVLAGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPT QPILEALDKDSSPKDDVWDSVSIISFPEKEQEDVLQTL **(SEQ ID NO: 88)**
scIFN-γ	IFNGR1	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVAD NGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVE TIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQV MAELGANVSGEFVKEAENLKKYFNAGHSDVADNGTLFLGILKNW KEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFN SNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAAKTGK RKRSQMLFRGSGGGSGGGGSGGGGSGGGGSGGGSLQEMGTADLG PSSVPTPTNVTIESYNMNPIVYWEYQIMPQVPVFTVEVKNYGVKNS EWIDACINISHHYCNISDHVGDPSNSLWVRVKARVGQKESAYAKSE EFAVCRDGKIGPPKLDIRKEEKQIMIDIFHPSVFVNGDEQEVDYDPE TTCYIRVYNVYVRMNGSEIQYKILTQKEDDCDEIQCQLAIPVSSLNS QYCVSAEGVLHVWGVTTEKSKEVCITIFNSSIKGSLWIPVVAALLLF LVLSLVFICFYIKKINPLKEKSIILPKSLISVVRSATLETKPESKYVSLIT SYQPFSLEKEVVCEEPLSPATVPGMHTEDNPGKVEHTEELSSITEVV TTEENIPDVVPGSHLTPIERESSSPLSSNQSEPGSIALNSYHSRNCSES DHSRNGFDTDSSCLESHSSLSDSEFPPNNKGEIKTEGQELITVIKAPT SFGYDKPHVLVDLLVDDSGKESLIGYRPTEDSKEFS **(SEQ ID NO: 89)**
scIFN-γ	IFNGR2	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVAD NGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVE TIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQV MAELGANVSGEFVKEAENLKKYFNAGHSDVADNGTLFLGILKNW KEESDRKIMQSQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFN SNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAAKTGK RKRSQMLFRGSGGGSGGGGSGGGGSGGGGSGGGSLQAPPDPLSQL PAPQHPKIRLYNAEQVLSWEPVALSNSTRPVVYQVQFKYTDSKWFT ADIMSIGVNCTQITATECDFTAASPSAGFPMDFNVTLRLRAELGALH SAWVTMPWFQHYRNVTVGPPENIEVTPGEGSLIIRFSSPFDIADTST AFFCYYVHYWEKGGIQQVKGPFRSNSISLDNLKPSRVYCLQVQAQ LLWNKSNIFRVGHLSNISCYETMADASTELQQVILISVGTFSLLSVL AGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPTQPILEALDKDS SPKDDVWDSVSIISFPEKEQEDVLQTL **(SEQ ID NO: 90)**
TNF-α	TNFR1	MALPVTALLLPLALLLHAARPVRSSSRTPSDKPVAHVVANPQAEGQ LQWLNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCP STHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPI YLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALSGGGSGG GGSGGGGSGGGGSGGGSLQLVPHLGDREKRDSVCPQGKYIHPQNN SICCTKCHKGTYLYNDCPGPGQDTDCRECESGSFTASENHLRHCLS CSKCRKEMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQCFNC SLCLNGTVHLSCQEKQNTVCTCHAGFFLRENECVSCSNCKKSLECT KLCLPQIENVKGTEDSGTTVLLPLVIFFGLCLLSLLFIGLMYRYQRW

		KSKLYSIVCGKSTPEKEGELEGTTTKPLAPNPSFSPTPGFTPTLGFSP VPSSTFTSSSTYTPGDCPNFAAPRREVAPPYQGADPILATALASDPIP NPLQKWEDSAHKPQSLDTDDPATLYAVVENVPPLRWKEFVRRLGLS DHEIDRLELQNGRCLREAQYSMLATWRRRTPRREATLELLGRVLRD MDLLGCLEDIEEALCGPAALPPAPSLLR **(SEQ ID NO: 91)**
TNF-α	TNFR2	MALPVTALLLPLALLLHAARPVRSSSRTPSDKPVAHVVANPQAEGQ LQWLNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCP STHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPI YLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALSGGGSGG GGSGGGGSGGGGSGGGSLQLPAQVAFTPYAPEPGSTCRLREYYDQT AQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWNWVPECL SCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPL RKCRPGFGVARPGTETSDVVCKPCAPGTFSNTTSSTDICRPHQICNV VAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPVSTRSQHTQPTPEPS TAPSTSFLLPMGPSPPAEGSTGDFALPVGLIVGVTALGLLIIGVVNCVI MTQVKKKPLCLQREAKVPHLPADKARGTQGPEQQHLLITAPSSSSS SLESSASALDRRAPTRNQPQAPGVEASGAGEARASTGSSDSSPGGH GTQVNVTCIVNVCSSSDHSSQCSSQASSTMGDTDSSPSESPKDEQVP FSKEECAFRSQLETPETLLGSTEEKPLPLGVPDAGMKPS **(SEQ ID NO: 92)**
IL-1β	IL-1R1	MALPVTALLLPLALLLHAARPAPVRSLNCTLRDSQQKSLVMSGPYE LKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLS CVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQ FPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSSGGGSGGG GSGGGGSGGGGSGGGSLQLEADKCKEREEKIILVSSANEIDVRPCPL NPNEHKGTITWYKDDSKTPVSTEQASRIHQHKEKLWFVPAKVEDS GHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKLPVAGD GGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIV MNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVS PANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGE DYYSVENPANKRRSTLITVLNISEIESRFYKHPFTCFAKNTHGIDAAY IQLIYPVTNFQKHMIGICVTLTVIIVCSVFIYKIFKIDIVLWYRDSCYD FLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEKQCG YKLFIYGRDDYVGEDIVEVINENVKKSRRLIIILVRETSGFSWLGGSS EEQIAMYNALVQDGIKVVLLELEKIQDYEKMPESIKFIKQKHGAIR WSGDFTQGPQSAKTRFWKNVRYHMPVQRRSPSSKHQLLSPATKEK LQREAHVPLG **(SEQ ID NO: 93)**
IL-1β	IL-1R3	MALPVTALLLPLALLLHAARPAPVRSLNCTLRDSQQKSLVMSGPYE LKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLS CVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQ FPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSSGGGSGGG GSGGGGSGGGGSGGGSLQSERCDDWGLDTMRQIQVFEDEPARIKC PLFEHFLKFNYSTAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKE KDVLWFRPTLLNDTGNYTCMLRNTTYCSKVAFPLEVVQKDSCFNS PMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWYMGCYKIQNF NNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVV

		GSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVW WTIDGKKPDDITIDVTINESISHSRTEDETRTQILSIKKVTSEDLKRSY VCHARSAKGEVAKAAKVKQKVPAPRYTVELACGFGATVLLVVILIV VYHVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAEEEEFV LLTLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSFIQKSRRLLVVLS PNYVLQGTQALLELKAGLENMASRGNINVILVQYKAVKETKVKEL KRAKTVLTVIKWKGEKSKYPQGRFWKQLQVAMPVKKSPRRSSSDE QGLSYSSLKNV **(SEQ ID NO: 94)**
cpIL-1β (89/88)	IL-1R1	MALPVTALLLPLALLLHAARPNYPKKKMEKRFVFNKIEINNKLEFE SAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSGGGGS GGGGSGGGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQD MEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQ LESVDPKSGGGSGGGGSGGGGSGGGGSGGGSLQLEADKCKEREEK IILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIHQH KEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYN AQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLL LDNIHFSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIE FITLEENKPTRPVIVSPANETMEVDLGSQIQLICNVTGQLSDIAYWK WNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNISEIESRFYKH PFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCSVFIYK IFKIDIVLWYRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDI FVFKVLPEVLEKQCGYKLFIYGRDDYVGEDIVEVINENVKKSRRLIII LVRETSGFSWLGGSSEEQIAMYNALVQDGIKVVLLELEKIQDYEKM PESIKFIKQKHGAIRWSGDFTQGPQSAKTRFWKNVRYHMPVQRRSP SSKHQLLSPATKEKLQREAHVPLG **(SEQ ID NO: 95)**
cpIL-1β (89/88)	IL-1R3	MALPVTALLLPLALLLHAARPNYPKKKMEKRFVFNKIEINNKLEFE SAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSGGGGS GGGGSGGGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQD MEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQ LESVDPKSGGGSGGGGSGGGGSGGGGSGGGSLQSERCDDWGLDT MRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLIWYWTRQDR DLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRNTTYCSK VAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSV KPTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPE NGRTFHLTRTLTVKVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIP CTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTINESISHSRTEDETRT QILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPRYTVE LACGFGATVLLVVILIVVYHVYWLEMVLFYRAHFGTDETILDGKEY DIYVSYARNAEEEEFVLLTLRGVLENEFGYKLCIFDRDSLPGGIVTD ETLSFIQKSRRLLVVLSPNYVLQGTQALLELKAGLENMASRGNINVI LVQYKAVKETKVKELKRAKTVLTVIKWKGEKSKYPQGRFWKQLQ VAMPVKKSPRRSSSDEQGLSYSSLKNV **(SEQ ID NO: 96)**
IL-6	IL-6Rα	MALPVTALLLPLALLLHAARPVPPGEDSKDVAAPHRQPLTSSERIDK QIRYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDGC FQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTK VLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLI

		LRSFKEFLQSSLRALRQMSGGGSGGGGSGGGGSGGGGSGGGSLQL APRRCPAQEVARGVLTSLPGDSVTLTCPGVEPEDNATVHWVLRKPA AGSHPSRWAGMGRRLLLRSVQLHDSGNYSCYRAGRPAGTVHLLVD VPPEEPQLSCFRKSPLSNVVCEWGPRSTPSLTTKAVLLVRKFQNSPA EDFQEPCQYSQESQKFSCQLAVPEGDSSFYIVSMCVASSVGSKFSKT QTFQGCGILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSFYRL RFELRYRAERSKTFTTWMVKDLQHHCVIHDAWSGLRHVVQLRAQ EEFGQGEWSEWSPEAMGTPWTESRSPPAENEVSTPMQALTTNKDD DNILFRDSANATSLPVQDSSSVPLPTFLVAGGSLAFGTLLCIAIVLRF KKTWKLRALKEGKTSMHPPYSLGQLVPERPRPTPVLVPLISPPVSPS SLGSDNTSSHNRPDARDPRSPYDISNTDYFFPR **(SEQ ID NO: 97)**
IL-6	gp130	MALPVTALLLPLALLLHAARPVPPGEDSKDVAAPHRQPLTSSERIDK QIRYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDGC FQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTK VLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLI LRSFKEFLQSSLRALRQMSGGGSGGGGSGGGGSGGGGSGGGSLQE LLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKT NHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGIT IISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWAT HKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALGKVTSDH INFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQ YRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGK GYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWK TLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLA TLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEW TTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAES KCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAV LEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTS DTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFL LTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPRHNFN SKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLFKKEKINTEG HSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQ VPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFK QNCSQHESSPDISHFERSKQVSSVNEEDFVRLKQQISDHISQSCGSG QMKMFQEVSAADAFGPGTEGQVERFETVGMEAATDEGMPKSYLP QTVRQGGYMPQ **(SEQ ID NO: 98)**
scIL-12	IL-12-Rβ1	MALPVTALLLPLALLLHAARPIWELKKDVYVVELDWYPDAPGEM VVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCH KGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYS GRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGD NKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIR DIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQV QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWA SVPCSGSTSGSGKPGSGEGSTKGRNLPVATPDPGMFPCLHHSQNLLR AVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKN ESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKT

		MNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEP DFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASSGGGSGGGGSGGGG SGGGGSGGGSLQCRTSECCFQDPPYPDADSGSASGPRDLRCYRISSD RYECSWQYEGPTAGVSHFLRCCLSSGRCCYFAAGSATRLQFSDQAG VSVLYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEPPLGDIKVSK LAGQLRMEWETPDNQVGAEVQFRHRTPSSPWKLGDCGPQDDDTE SCLCPLEMNVAQEFQLRRRQLGSQGSSWSKWSSPVCVPPENPPQPQ VRFSVEQLGQDGRRRLTLKEQPTQLELPEGCQGLAPGTEVTYRLQL HMLSCPCKAKATRTLHLGKMPYLSGAAYNVAVISSNQFGPGLNQT WHIPADTHTEPVALNISVGTNGTTMYWPARAQSMTYCIEWQPVGQ DGGLATCSLTAPQDPDPAGMATYSWSRESGAMGQEKCYYITIFASA HPEKLTLWSTVLSTYHFGGNASAAGTPHHVSVKNHSLDSVSVDWA PSLLSTCPGVLKEYVVRCRDEDSKQVSEHPVQPTETQVTLSGLRAG VAYTVQVRADTAWLRGVWSQPQRFSIEVQVSDWLIFFASLGSFLSIL LVGVLGYLGLNRAARHLCPPLPTPCASSAIEFPGGKETWQWINPVD FQEEASLQEALVVEMSWDKGERTEPLEKTELPEGAPELALDTELSL EDGDRCKAKM **(SEQ ID NO: 99)**
scIL-12	IL-12-Rβ2	MALPVTALLLPLALLLHAARPIWELKKDVYVVELDWYPDAPGEM VVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCH KGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYS GRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGD NKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIR DIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQV QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWA SVPCSGSTSGSGKPGSGEGSTKGRNLPVATPDPGMFPCLHHSQNLLR AVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKN ESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKT MNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEP DFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASSGGGSGGGGSGGGG SGGGGSGGGSLQKIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQ GCFHYSRRNKLILYKFDRRINFHHGHSLNSQVTGLPLGTTLFVCKLA CINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQGTVACTWERGRDT HLYTEYTLQLSGPKNLTWQKQCKDIYCDYLDFGINLTPESPESNFTA KVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQKASVSRCTLYW RDEGLVLLNRLRYRPSNSRLWNMVNVTKAKGRHDLLDLKPFTEYE FQISSKLHLYKGSWSDWSESLRAQTPEEEPTGMLDVWYMKRHIDY SRQQISLFWKNLSVSEARGKILHYQVTLQELTGGKAMTQNITGHTS WTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGLLAPRQVSA NSEGMDNILVTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNW LRSRPYNVSALISENIKSYICYEIRVYALSGDQGGCSSILGNSKHKAP LSGPHINAITEEKGSILISWNSIPVQEQMGCLLHYRIYWKERDSNSQP QLCEIPYRVSQNSHPINSLQPRVTYVLWMTALTAAGESSHGNEREFC LQGKANWMAFVAPSICIAIIMVGIFSTHYFQQKVFVLLAALRPQWC SREIPDPANSTCAKKYPIAEEKTQLPLDRLLIDWPTPEDPEPLVISEVL HQVTPVFRHPPCSNWPQREKGIQGHQASEKDMMHSASSPPPPRAL QAESRQLVDLYKVLESRGSDPKPENPACPWTVLPAGDLPTHDGYLP

		SNIDDLPSHEAPLADSLEELEPQHISLSVFPSSSLHPLTFSCGDKLTLD QLKMRCDSLML **(SEQ ID NO: 100)**
IL-4	IL-4Rα	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTEL TVTDIFAASKNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQF HRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTI MREKYSKCSSSGGGSGGGGSGGGGSGGGGSGGGSLQMKVLQEPT CVSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENN GGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKP RAPGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDP ADFRIYNVTYLEPSLRIAASTLKSGISYRARVRAWAQCYNTTWSEW SPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKEW WDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTK LLPCFLEHNMKRDEDPHKAAKEMPFQGSGKSAWCPVEISKTVLWP ESISVVRCVELFEAPVECEEEEEVEEEKGSFCASPESSRDDFQEGRE GIVARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWD EFPSAGPKEAPPWGKEQPLHLEPSPPASPTQSPDNLTCTETPLVIAGN PAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTTV PQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGT QASAVVGLGPPGEAGYKAFSSLLASSAVSPEKCGFGASSGEEGYKP FQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLGLEP GEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCH GQEDGGQTPVMASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLEAS LCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTYM RVS **(SEQ ID NO: 101)**
IL-4	IL-2Rγc	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTEL TVTDIFAASKNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQF HRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTI MREKYSKCSSSGGGSGGGGSGGGGSGGGGSGGGSLQLNTTILTPN GNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSS SEPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIH LYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKLSESQ LELNWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSV DGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENPFLFA LEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGN FSAWSGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQ HSPYWAPPCYTLKPET **(SEQ ID NO: 102)**
IL-4	IL-13Ra1	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTEL TVTDIFAASKNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQF HRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTI MREKYSKCSSSGGGSGGGGSGGGGSGGGGSGGGSLQGGGGAAPT ETQPPVTNLSVSVENLCTVIWTWNPPEGASSNCSLWYFSHFGDKQD KKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEGD PESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKI HQCENIFREGQYFGCSFDLTKVKDSSFEQHSVQIMVKDNAGKIKPSF NIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFYEVEV NNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNT

		VRIRVKTNKLCYEDDKLWSNWSQEMSIGKKRNSTLYITMLLIVPVI VAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWKKYDI YEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 103)**
cpIL-4 (38-37)	IL-4Rα	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKD TRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQS TLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTEQ KTLCTELTVTDIFAASKSGGGSGGGGSGGGGSGGGGSGGGSLQMK VLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHT CIPENNGGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKP SEHVKPRAPGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNI WSENDPADFRIYNVTYLEPSLRIAASTLKSGISYRARVRAWAQCYN TTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSIT KIKKEWWDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHW KNCLTKLLPCFLEHNMKRDEDPHKAAKEMPFQGSGKSAWCPVEIS KTVLWPESISVVRCVELFEAPVECEEEEEVEEEKGSFCASPESSRDD FQEGREGIVARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSA HMPWDEFPSAGPKEAPPWGKEQPLHLEPSPPASPTQSPDNLTCTETP LVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQL SEPTTVPQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAV EQGGTQASAVVGLGPPGEAGYKAFSSLLASSAVSPEKCGFGASSGE EGYKPFQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPE HLGLEPGEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCG HLKQCHGQEDGGQTPVMASPCCGCCCGDRSSPPTTPLRAPDPSPG GVPLEASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVS VGPTYMRVS **(SEQ ID NO: 104)**
cpIL-4 (38-37)	IL-2Rγc	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKD TRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQS TLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTEQ KTLCTELTVTDIFAASKSGGGSGGGGSGGGGSGGGGSGGGSLQLNT TILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNC TWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQ KKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHK LSESQLELNWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKF SLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKE NPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVT EYHGNFSAWSGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPG ASPCNQHSPYWAPPCYTLKPET **(SEQ ID NO: 105)**
cpIL-4 (38-37)	IL-13Ra1	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKD TRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQS TLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTEQ KTLCTELTVTDIFAASKSGGGSGGGGSGGGGSGGGGSGGGSLQGG GGAAPTETQPPVTNLSVSVENLCTVIWTWNPPEGASSNCSLWYFSH FGDKQDKKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKC ISPPEGDPESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYW HRSLEKIHQCENIFREGQYFGCSFDLTKVKDSSFEQHSVQIMVKDN AGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRC

		LFYEVEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGV LPDTLNTVRIRVKTNKLCYEDDKLWSNWSQEMSIGKKRNSTLYITM LLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLH WKKYDIYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 106)**
IL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSG GGSGGGGSGGGGSGGGGSGGGSLQHGTELPSPPSVWFEAEFFHHIL HWTPIPNQSESTCYEVALLRYGIESWNSISNCSQTLSYDLTAVTLDLY HSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHN GFILGKIQLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTHKK VKHENFSLLTSGEVGEFCVQVKPSVASRSNKGMWSKEECISLTRQY FTVTNVIIFFAFVLLLSGALAYCLALQLYVRRRKKLPSVLLFKKPSPF IFISQRPSPETQDTIHPLDEEAFLKVSPELKNLDLHGSTDSGFGSTKPS LQTEEPQFLLPDPHPQADRTLGNREPPVLGDSCSSGSSNSTDSGICL QEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGS ALGHHSPPEPEVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEE SPLTDGLGPKFGRCLVDEAGLHPPALAKGYLKQDPLEMTLASSGAP TGQWNQPTEEWSLLALSSCSDLGISDWSFAHDLAPLGCVAAPGGLL GSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 107)**
IL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSG GGSGGGGSGGGGSGGGGSGGGSLQMVPPPENVRMNSVNFKNILQ WESPAFAKGNLTFTAQYLSYRIFQDKCMNTTLTECDFSSLSKYGDH TLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRF LAPKIENEYETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDF EVLRNLEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQTTHDETVPS WMVAVILMASVFMVCLALLGCFALLWCVYKKTKYAFSPRNSLPQH LKEFLGHPHHNTLLFFSFPLSDENDVFDKLSVIAEDSESGKQNPGDS CSLGTPPGQGPQS **(SEQ ID NO: 108)**
mIL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN GGGSGGKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMT MKIRNSGGGSGGGGSGGGGSGGGGSGGGSLQHGTELPSPPSVWFE AEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSISNCSQTLSYDL TAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVG SVNLEIHNGFILGKIQLPRPKMAPANDTYESIFSHFREYEIAIRKVPG NFTFTHKKVKHENFSLLTSGEVGEFCVQVKPSVASRSNKGMWSKE ECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYVRRRKKLPSV LLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLKVSPELKNLDLHGSTD SGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPPVLGDSCSSGSS NSTDSGICLQEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGR

		AGDTQGGSALGHHSPPEPEVPGEEDPAAVAFQGYLRQTRCAEEKAT KTGCLEEESPLTDGLGPKFGRCLVDEAGLHPPALAKGYLKQDPLEM TLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSFAHDLAPLGC VAAPGGLLGSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 109)**
mIL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN GGGSGGKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMT MKIRNSGGGSGGGGSGGGGSGGGGSGGGSLQMVPPPENVRMNSV NFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMNTTLTECDFSSL SKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLAD SLHMRFLAPKIENEYETWTMKNVYNSWTYNVQYWKNGTDEKFQI TPQYDFEVLRNLEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQTTH DETVPSWMVAVILMASVFMVCLALLGCFALLWCVYKKTKYAFSPR NSLPQHLKEFLGHPHHNTLLFFSFPLSDENDVFDKLSVIAEDSESGK QNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 110)**
cpIL-10 (58/57)	IL-10R1	MALPVTALLLPLALLLHAARPGYLGCQALSEMIQFYLEEVMPQAE NQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKN AFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGG GGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQ LDNLLLKESLLEDFKSGGGSGGGGSGGGGSGGGGSGGGSLQHGTE LPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSIS NCSQTLSYDLTAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNTRFS VDEVTLTVGSVNLEIHNGFILGKIQLPRPKMAPANDTYESIFSHFRE YEIAIRKVPGNFTFTHKKVKHENFSLLTSGEVGEFCVQVKPSVASRS NKGMWSKEECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYV RRRKKLPSVLLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLKVSPELK NLDLHGSTDSGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPPVL GDSCSSGSSNSTDSGICLQEPSLSPSTGPTWEQQVGSNSRGQDDSGI DLVQNSEGRAGDTQGGSALGHHSPPEPEVPGEEDPAAVAFQGYLRQ TRCAEEKATKTGCLEEESPLTDGLGPKFGRCLVDEAGLHPPALAKG YLKQDPLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSF AHDLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 111)**
cpIL-10 (58/57)	IL-10R2	MALPVTALLLPLALLLHAARPGYLGCQALSEMIQFYLEEVMPQAE NQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKN AFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGG GGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQ LDNLLLKESLLEDFKSGGGSGGGGSGGGGSGGGGSGGGSLQMVPP PENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMNT TLTECDFSSLSKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIGPP GMQVEVLADSLHMRFLAPKIENEYETWTMKNVYNSWTYNVQYW KNGTDEKFQITPQYDFEVLRNLEPWTTYCVQVRGFLPDRNKAGEW SEPVCEQTTHDETVPSWMVAVILMASVFMVCLALLGCFALLWCVY KKTKYAFSPRNSLPQHLKEFLGHPHHNTLLFFSFPLSDENDVFDKLS VIAEDSESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 112)**

tdIL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGG GGSGGGGSGGGGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSR VKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVM PQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQ VKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGG SGGGGSGGGGSGGGSLQHGTELPSPPSVWFEAEFFHHILHWTPIPN QSESTCYEVALLRYGIESWNSISNCSQTLSYDLTAVTLDLYHSNGYR ARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHNGFILGKI QLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTHKKVKHENF SLLTSGEVGEFCVQVKPSVASRSNKGMWSKEECISLTRQYFTVTNVI IFFAFVLLLSGALAYCLALQLYVRRRKKLPSVLLFKKPSPFIFISQRPS PETQDTIHPLDEEAFLKVSPELKNLDLHGSTDSGFGSTKPSLQTEEP QFLLPDPHPQADRTLGNREPPVLGDSCSSGSSNSTDSGICLQEPSLSP STGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSALGHHS PPEPEVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEESPLTDGL GPKFGRCLVDEAGLHPPALAKGYLKQDPLEMTLASSGAPTGQWNQ PTEEWSLLALSSCSDLGISDWSFAHDLAPLGCVAAPGGLLGSFNSDL VTLPLISSLQSSE **(SEQ ID NO: 113)**
tdIL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRD LRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQF YLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGG GGSGGGGSGGGGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSR VKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVM PQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQ VKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGG SGGGGSGGGGSGGGSLQMVPPPENVRMNSVNFKNILQWESPAFAK GNLTFTAQYLSYRIFQDKCMNTTLTECDFSSLSKYGDHTLRVRAEF ADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLAPKIENE YETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDFEVLRNLEP WTTYCVQVRGFLPDRNKAGEWSEPVCEQTTHDETVPSWMVAVIL MASVFMVCLALLGCFALLWCVYKKTKYAFSPRNSLPQHLKEFLGH PHHNTLLFFSFPLSDENDVFDKLSVIAEDSESGKQNPGDSCSLGTPP GQGPQS **(SEQ ID NO: 114)**
IL-13	IL-13Rα1	MALPVTALLLPLALLLHAARPLTCLGGFASPGPVPPSTALRELIEELV NITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQ RMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREG RFNSGGGSGGGGSGGGGSGGGGSGGGSLQGGGGAAPTETQPPVTN LSVSVENLCTVIWTWNPPEGASSNCSLWYFSHFGDKQDKKIAPETR RSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEGDPESAVTEL QCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIF REGQYFGCSFDLTKVKDSSFEQHSVQIMVKDNAGKIKPSFNIVPLTS RVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFYEVEVNNSQTE

		THNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNTVRIRVKT NKLCYEDDKLWSNWSQEMSIGKKRNSTLYITMLLIVPVIVAGAIIVL LLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWKKYDIYEKQTK EETDSVVLIENLKKASQ **(SEQ ID NO: 115)**
IL-13	IL-4Rα	MALPVTALLLPLALLLHAARPLTCLGGFASPGPVPPSTALRELIEELV NITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQ RMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREG RFNSGGGSGGGGSGGGGSGGGGSGGGSLQMKVLQEPTCVSDYMSI STCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENNGGAGCVCH LLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPRAPGNLTV HTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNV TYLEPSLRIAASTLKSGISYRARVRAWAQCYNTTWSEWSPSTKWHN SYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKEWWDQIPNPAR SRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLLPCFLEHN MKRDEDPHKAAKEMPFQGSGKSAWCPVEISKTVLWPESISVVRCV ELFEAPVECEEEEEVEEEKGSFCASPESSRDDFQEGREGIVARLTESL FLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKE APPWGKEQPLHLEPSPPASPTQSPDNLTCTETPLVIAGNPAYRSFSNS LSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTTVPQPEPETW EQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGL GPPGEAGYKAFSSLLASSAVSPEKCGFGASSGEEGYKPFQDLIPGCP GDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLGLEPGEKVEDMP KPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQT PVMASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLEASLCPASLAPS GISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTYMRVS **(SEQ ID NO: 116)**
cpIL-13 (75/74)	IL-13Rα1	MALPVTALLLPLALLLHAARPVSAGQFSSLHVRDTKIEVAQFVKDL LLHLKKLFREGRFNGGGGSLTCLGGFASPGPVPPSTALRELIEELVNI TQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQR MLSGFCPHKSGGGSGGGGSGGGGSGGGGSGGGSLQGGGGAAPTE TQPPVTNLSVSVENLCTVIWTWNPPEGASSNCSLWYFSHFGDKQD KKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEGD PESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKI HQCENIFREGQYFGCSFDLTKVKDSSFEQHSVQIMVKDNAGKIKPS FNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFYEVE VNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLN TVRIRVKTNKLCYEDDKLWSNWSQEMSIGKKRNSTLYITMLLIVPVI VAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWKKYD IYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 117)**
cpIL-13 (75/74)	IL-4Rα	MALPVTALLLPLALLLHAARPVSAGQFSSLHVRDTKIEVAQFVKDL LLHLKKLFREGRFNGGGGSLTCLGGFASPGPVPPSTALRELIEELVNI TQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQR MLSGFCPHKSGGGSGGGGSGGGGSGGGGSGGGSLQMKVLQEPTC VSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENNG GAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPR APGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPA

		DFRIYNVTYLEPSLRIAASTLKSGISYRARVRAWAQCYNTTWSEWS PSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKEWW DQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLL PCFLEHNMKRDEDPHKAAKEMPFQGSGKSAWCPVEISKTVLWPESI SVVRCVELFEAPVECEEEEEVEEEKGSFCASPESSRDDFQEGREGIV ARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFP SAGPKEAPPWGKEQPLHLEPSPPASPTQSPDNLTCTETPLVIAGNPAY RSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTTVPQP EPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQAS AVVGLGPPGEAGYKAFSSLLASSAVSPEKCGFGASSGEEGYKPFQD LIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLGLEPGEK VEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQE DGGQTPVMASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLEASLCP ASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTYMRVS **(SEQ ID NO: 118)**
IL-18	IL-18Rα	MALPVTALLLPLALLLHAARPYFGKLESKLSVIRNLNDQVLFIDQG NRPLFEDMTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKIS TLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSSY EGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGGGSGGGG SGGGGSGGGGSGGGSLQAESCTSRPHITVVEGEPFYLKHCSCSLAH EIETTTKSWYKSSGSQEHVELNPRSSSRIALHDCVLEFWPVELNDTG SYFFQMKNYTQKWKLNVIRRNKHSCFTERQVTSKIVEVKKFFQITC ENSYYQTLVNSTSLYKNCKKLLLENNKNPTIKKNAEFEDQGYYSCV HFLHHNGKLFNITKTFNITIVEDRSNIVPVLLGPKLNHVAVELGKNV RLNCSALLNEEDVIYWMFGEENGSDPNIHEEKEMRIMTPEGKWHA SKVLRIENIGESNLNVLYNCTVASTGGTDTKSFILVRKADMADIPGH VFTRGMIIAVLILVAVVCLVTVCVIYRVDLVLFYRHLTRRDETLTDGK TYDAFVSYLKECRPENGEEHTFAVEILPRVLEKHFGYKLCIFERDVV PGGAVVDEIHSLIEKSRRLIIVLSKSYMSNEVRYELESGLHEALVERK IKIILIEFTPVTDFTFLPQSLKLLKSHRVLKWKADKSLSYNSRFWKNL LYLMPAKTVKPGRDEPEVLPVLSES **(SEQ ID NO: 119)**
IL-18	IL-18Rβ	MALPVTALLLPLALLLHAARPYFGKLESKLSVIRNLNDQVLFIDQG NRPLFEDMTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKIS TLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSSY EGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGGGSGGGG SGGGGSGGGGSGGGSLQFNISGCSTKKLLWTYSTRSEEEFVLFCDL PEPQKSHFCHRNRLSPKQVPEHLPFMGSNDLSDVQWYQQPSNGDP LEDIRKSYPHIIQDKCTLHFLTPGVNNSGSYICRPKMIKSPYDVACCV KMILEVKPQTNASCEYSASHKQDLLLGSTGSISCPSLSCQSDAQSPA VTWYKNGKLLSVERSNRIVVDEVYDYHQGTYVCDYTQSDTVSSW TVRAVVQVRTIVGDTKLKPDILDPVEDTLEVELGKPLTISCKARFGF ERVFNPVIKWYIKDSDLEWEVSVPEAKSIKSTLKDEIIERNIILEKVT QRDLRRKFVCFVQNSIGNTTQSVQLKEKRGVVLLYILLGTIGTLVAV LAASALLYRHWIEIVLLYRTYQSKDQTLGDKKDFDAFVSYAKWSSF PSEATSSLSEEHLALSLFPDVLENKYGYSLCLLERDVAPGGVYAEDI VSIIKRSRRGIFILSPNYVNGPSIFELQAAVNLALDDQTLKLILIKFCY

		FQEPESLPHLVKKALRVLPTVTWRGLKSVPPNSRFWAKMRYHMPV KNSQGFTWNQLRITSRIFQWKGLSRTETTGRSSQPKEW **(SEQ ID NO: 120)**

Table 10 – Codon Optimized DNA Sequences for Full Constructs (all constructs designed with representative signal peptide (CD8a) and flexible linker (linker 26))

Cytokine	Receptor	Codon Optimized Sequence
IFN-α2	IFNAR1	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgtgcgacct tccacagacccattccctcggctctcgaagaactctgatgttgctggcccagatgcggaagatttctcttttct catgtctgaaagacaggcacgactttggttttccccaggaggagttcggaaaccagttccagaaagcgga aaccattcctgtgctgcacgaaatgatccaacaaattttcaacctgttttcaactaaagatagctccgctgcat gggacgagacactcctcgataagttttatacagagctttaccagcagttaaatgatctggaagcttgtgtcat ccaaggggtcggcgtaaccgagacgcccctgatgaaggaggatagcatactggcagtgcggaagtactt ccagaggatcaccctctatctaaaggaaaaaaagtacagtccgtgcgcctgggaagtggttagagccgaa atcatgcgtagcttttccttatctacaaatttgcaggagtcgttgcgcagtaaagagtctggaggcggaagc gggggtggcggcagcggcggtggaggatcaggtggcgggggggtccgggggcggaagtctgcagaa gaacctgaaatccccacagaaagtcgaggtggacatcatcgatgacaatttcatcttaagatggaaccgta gcgatgagtccgtcggaaatgtcacattttcttttgattatcagaagaccgggatggacaactggattaagct gtccggttgccagaacataaccagtaccaagtgtaacttcagcagcctcaaactcaatgtatatgaggaaat caagctgaggatccgggccgagaaggaaaacacaagctcctggtatgaagttgattcatttactccatttcg aaaagcgcaaataggacccccggaagttcacctcgaggctgaagataaagcaattgtaatacacatatcg cctggcaccaaggactctgtgatgtgggctttagatgggctgtcattcacgtacagcctggtgatctggaag aacagttctggggtggaggagagaatagaaaacatttatagtcgccacaaaatctacaaattgtcacccga aacaacctattgcctgaaggtcaaggcggcactattgacgtcctggaagatcggcgtgtactcaccagtgc attgtataaagacaacagtggaaaacgagcttcccccgccggagaatattgaggtttccgtgcagaatcag aattatgtgttgaagtgggactacacatatgccaatatgaccttccaggttcaatggcttcatgcatttctgaaa agaaaccctggtaaccacctttacaaatggaagcagattcctgactgcgagaatgtcaagaccacacagtg cgtgtttcctcaaaacgttttccagaaaggcatctatctgctacgggtccaggcttccgatggcaataatacct cattttggagcgaggaaattaaattcgacactgaaatccaagccttcctactccctcccgtatttaacatcagg agtctgtctgatagcttccatatttacatcggtgctcccaagcagtctggaaacactcccgtgatccaggatta ccccctcatctacgagatcattttctgggaaaacacctctaacgccgaacggaagattatagagaagaaaa ctgacgtcactgtgcctaacctgaaaccattaactgtctattgcgtcaaagctagggcccacaccatggatg aaaaactgaacaagtctagcgtgttcagcgacgcagtttgtgagaaaacgaagccaggaaatacttctaag atttggcttatcgtgggcatttgtatcgctctgttcgcactgccctttgtaatctacgccgccaaggtttttctcc gctgtattaattatgtgtttttcccatccctgaagccatcatcgtcgattgacgagtacttctctgagcaacctct taaaaacctgttgttgtccaccagtgaagagcagattgagaaatgcttcattatcgaaaatatttcaacaatcg ccacagtggaggagacgaatcagaccgacgaggaccataagaagtacagcagtcagacatctcaggatt ccgggaattacagcaatgaagatgaaagtgaatccaaaactagcgaggagctccaacaggactttgtg **(SEQ ID NO: 121)**
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IL-6	IL-6Rα	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccggtgccgc ccggggaagatagcaaggatgtggctgctcctcacaggcagccactgacaagcagcgagagaatcgac aagcaaataaggtatattcttgatggaatcagcgcgctgcgaaaggagacatgtaacaagtcgaatatgtg cgagtcttccaaagaagcacttgctgaaaataatctgaacctcccaaaaatggccgagaaagacggctgct ttcagtccggttttaacgaggagacttgtttagtaaagattataacgggcttgttggaattcgaagtctacctag aatacctccaaaatagattcgagagtagtgaggaacaggcccgcgctgttcagatgtcaacaaaagtgttg atccaattcctgcagaaaaaagccaagaacttagatgcaatcaccacacctgaccccactaccaatgcctct ctgctcaccaagctgcaagcccagaaccagtggctgcaggacatgactacccatctaattctgcggtctttt aaggagttcctccagtcatccctgcgtgcacttcggcagatgtctggaggcggaagcgggggtggcggc agcggcggtggaggatcaggtggcgggggtccgggggcggaagtctgcagcttgcaccaagacgct gtccggctcaggaggtcgctaggggagtgctgacctcgctgccgggcgactccgtgaccctgacatgtc ctggagtggagcctgaggacaacgcaacagttcactgggtgctacggaagcccgccgctggctcccatc cttccaggtgggccgggatggggcgcagactgcttctcagatcagtgcagttacatgatagcggtaattac agctgctaccgcgctggaaggccggcaggcactgtgcacctcctagtggatgttccacctgaggagcca cagttgagctgctttcgaaaaagtcccttgtctaacgtcgtatgcgagtggggccctagatcaactccctccc tcaccaccaaagcggttctcctcgtacgtaagttccaaaactctcctgccgaagattttcaagagccatgtca gtatagccaggagagtcagaagttctcatgccagcttgcagtcccggagggtgactcatccttctatattgtt agtatgtgcgtcgcctcgtctgtggggtctaagtttagcaagactcaaacttttcagggctgcggcatcctcc aaccagaccccccctgccaacattacagtgaccgcagttgccagaaaccctaggtggttgagcgtgacgtg gcaggatccccattcctggaattcatcattctacagactgcggttcgagctccgatacagggcggaacgta gcaagacattcaccacgtggatggtcaaagacctgcagcaccactgtgtaatccatgacgcttggagcgg tctgcgccacgtggtccagctgcgggcacaagaggaattcggacagggtgaatggagtgaatggtctcct gaggctatgggcactccgtggaccgaatctcggtctccaccagccgaaaacgaagtgtccacccctatgc aggctctgactactaataaggatgacgataatatcttgtttagggactccgcaaatgctacatcactgcctgta caggattccagtagtgttcccctaccaaccttttagtcgccggagggtctctggcgttcgggacgttgctct gtatagccattgtgctgcgtttcaaaaagacctggaaactgcgcgccttaaaggagggaaaaacaagcat gcacccccatattctcttgggcagctggtgcccgaacggcccagaccaacaccagtcctggtgcctctta tatccccccccgtgagcccctctagcctgggcagtgacaataccagtagccataataggcccgacgcccg agaccctcgctccccatacgatatctcaaacacagattatttttttccccgg **(SEQ ID NO: 135)**

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IL-13	IL-4Rα	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgttaacatgt ctgggcgggttcgcctcacctggaccagttccccccttcaaccgctctcagagaactgattgaggagctcgt caatatcacccagaaccaaaaagccccactctgcaatggaagtatggtgtggtctattaacttgactgccgg catgtactgtgccgcactggagtctttgatcaacgtgtccgggtgcagtgcaatcgaaaagacgcagcgg atgctgagcggcttttgccccccacaaggtgagcgctggtcagttttccagccttcacgtgcgagatacaaa gatagaagtagcgcagttcgtcaaggacctgctgctgcatcttaaaaaactatttcgcgagggtaggttcaa ttctggaggcggaagcgggggtggcggcagcggcggtggaggatcaggtggcgggggggtccggggg cggaagtctgcagatgaaagtgctgcaggaaccgacctgcgtgagcgattatatgagcattagcacctgc gaatggaaaatgaacggcccgaccaactgcagcaccgaactgcgcctgctgtatcagctggtgtttctgct gagcgaagcgcatacctgcattccggaaaacaacggcggcgcgggctgcgtgtgccatctgctgatgga tgatgtggtgagcgcggataactataccctggatctgtgggcgggccagcagctgctgtggaaaggcag ctttaaaccgagcgaacatgtgaaaccgcgcgcgccgggcaacctgaccgtgcataccaacgtgagcga taccctgctgctgacctggagcaacccgtatccgccggataactatctgtataaccatctgacctatgcggt gaacatttggagcgaaaacgatccggcggattttcgcatttataacgtgacctatctggaaccgagcctgcg cattgcggcgagcaccctgaaaagcggcattagctatcgcgcgcgcgtgcgcgcgtgggcgcagtgcta taacaccacctggagcgaatggagcccgagcaccaaatggcataacagctatcgcgaaccgtttgaaca gcatctgctgctgggcgtgagcgtgagctgcattgtgattctggcggtgtgcctgctgtgctatgtgagcatt accaaaattaaaaaagaatggtgggatcagattccgaacccggcgcgcagccgcctggtggcgattatta ttcaggatgcgcagggcagccagtgggaaaaacgcagccgcggccaggaaccggcgaaatgcccgc attggaaaaactgcctgaccaaactgctgccgtgctttctggaacataacatgaaacgcgatgaagatccg cataaagcggcgaaagaaatgccgtttcagggcagcggcaaaagcgcgtggtgcccggtggaaattag caaaaccgtgctgtggccggaaagcattagcgtggtgcgctgcgtggaactgtttgaagcgccggtggaa tgcgaagaagaagaagaagtggaagaagaaaaaggcagcttttgcgcgagcccggaaagcagccgcg atgattttcaggaaggccgcgaaggcattgtggcgcgcctgaccgaaagcctgtttctggatctgctgggc gaagaaaacggcggcttttgccagcaggatatgggcgaaagctgcctgctgccgccgagcggcagcac cagcgcgcatatgccgtgggatgaatttccgagcgcgggcccgaaagaagcgccgccgtggggcaaa gaacagccgctgcatctggaaccgagcccgccggcgagcccgacccagagcccggataacctgacct gcaccgaaaccccgctggtgattgcgggcaacccggcgtatcgcagctttagcaacagcctgagccaga gcccgtgcccgcgcgaactgggcccggatccgctgctggcgcgccatctggaagaagtggaaccgga aatgccgtgcgtgccgcagctgagcgaaccgaccaccgtgccgcagccggaaccggaaacctgggaa cagattctgcgccgcaacgtgctgcagcatggcgcggcggcggcgccggtgagcgcgccgaccagcg gctatcaggaatttgtgcatgcggtggaacagggcggcacccaggcgagcgcggtggtgggcctgggc ccgccgggcgaagcgggctataaagcgtttagcagcctgctggcgagcagcgcggtgagcccggaaa aatgcggctttggcgcgagcagcggcgaagaaggctataaaccgtttcaggatctgattccgggctgccc gggcgatccggcgccggtgccggtgccgctgtttacctttggcctggatcgcgaaccgccgcgcagccc gcagagcagccatctgccgagcagcagcccggaacatctgggcctggaaccgggcgaaaaagtggaa gatatgccgaaaccgccgctgccgcaggaacaggcgaccgatccgctggtggatagcctgggcagcg

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cpIL-13(75/74)	IL-13Rα1	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccggtgagcg cgggccagtttagcagcctgcatgtgcgcgataccaaaattgaagtggcgcagtttgtgaaagatctgctg ctgcatctgaaaaaactgtttcgcgaaggccgctttaacggaggaggtggatctctgacctgcctgggcgg ctttgcgagcccgggcccggtgccgccgagcaccgcgctgcgcgaactgattgaagaactggtgaacat tacccagaaccagaaagcgccgctgtgcaacggcagcatggtgtggagcattaacctgaccgcgggcat gtattgcgcggcgctggaaagcctgattaacgtgagcggctgcagcgcgattgaaaaaacccagcgcat gctgagcggcttttgcccgcataaatctggaggcggaagcgggggtggcggcagcggcggtggaggat caggtggcgggggggtccgggggcggaagtctgcagggcggcggcggcgcggcgccgaccgaaacc cagccgccggtgaccaacctgagcgtgagcgtggaaaacctgtgcaccgtgatttggacctggaacccg ccggaaggcgcgagcagcaactgcagcctgtggtattttagccattttggcgataaacaggataaaaaaat tgcgccggaaacccgccgcagcattgaagtgccgctgaacgaacgcatttgcctgcaggtgggcagcca gtgcagcaccaacgaaagcgaaaaaccgagcattctggtggaaaaatgcattagcccgccggaaggcg atccggaaagcgcggtgaccgaactgcagtgcatttggcataacctgagctatatgaaatgcagctggctg ccgggccgcaacaccagcccggataccaactataccctgtattattggcatcgcagcctggaaaaaattca tcagtgcgaaaacatttttcgcgaaggccagtattttggctgcagctttgatctgaccaaagtgaaagatagc agctttgaacagcatagcgtgcagattatggtgaaagataacgcgggcaaaattaaaccgagctttaacatt gtgccgctgaccagccgcgtgaaaccggatccgccgcatattaaaaacctgagctttcataacgatgatct gtatgtgcagtgggaaaacccgcagaactttattagccgctgcctgttttatgaagtggaagtgaacaacag ccagaccgaaacccataacgtgttttatgtgcaggaagcgaaatgcgaaaacccggaatttgaacgcaac gtggaaaacaccagctgctttatggtgccgggcgtgctgccggataccctgaacaccgtgcgcattcgcg tgaaaaccaacaaactgtgctatgaagatgataaactgtggagcaactggagccaggaaatgagcattgg caaaaaacgcaacagcaccctgtatattaccatgctgctgattgtgccggtgattgtggcgggcgcgattat tgtgctgctgctgtatctgaaacgcctgaaaattattatttttccgccgattccggatccgggcaaaatttttaa agaaatgtttggcgatcagaacgatgataccctgcattggaaaaaatatgatatttatgaaaaacagaccaa agaagaaaccgatagcgtggtgctgattgaaaacctgaaaaaagcgagccag **(SEQ ID NO: 155)**
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		tgacctatctggaaccgagcctgcgcattgcggcgagcaccctgaaaagcggcattagctatcgcgcgc gcgtgcgcgcgtgggcgcagtgctataacaccacctggagcgaatggagcccgagcaccaaatggcat aacagctatcgcgaaccgtttgaacagcatctgctgctgggcgtgagcgtgagctgcattgtgattctggc ggtgtgcctgctgtgctatgtgagcattaccaaaattaaaaaagaatggtgggatcagattccgaacccgg cgcgcagccgcctggtggcgattattattcaggatgcgcagggcagccagtgggaaaaacgcagccgc ggccaggaaccggcgaaatgcccgcattggaaaaactgcctgaccaaactgctgccgtgctttctggaac ataacatgaaacgcgatgaagatccgcataaagcggcgaaagaaatgccgtttcagggcagcggcaaaa gcgcgtggtgcccggtggaaattagcaaaaccgtgctgtggccggaaagcattagcgtggtgcgctgcg tggaactgtttgaagcgccggtggaatgcgaagaagaagaagaagtggaagaagaaaaaggcagctttt gcgcgagcccggaaagcagccgcgatgattttcaggaaggccgcgaaggcattgtggcgcgcctgacc gaaagcctgtttctggatctgctgggcgaagaaaacggcggcttttgccagcaggatatgggcgaaagct gcctgctgccgccgagcggcagcaccagcgcgcatatgccgtgggatgaatttccgagcgcgggcccg aaagaagcgccgccgtggggcaaagaacagccgctgcatctggaaccgagcccgccggcgagcccg acccagagcccggataacctgacctgcaccgaaaccccgctggtgattgcgggcaacccggcgtatcgc agctttagcaacagcctgagccagagcccgtgcccgcgcgaactgggcccggatccgctgctggcgcg ccatctggaagaagtggaaccggaaatgccgtgcgtgccgcagctgagcgaaccgaccaccgtgccgc agccggaaccggaaacctgggaacagattctgcgccgcaacgtgctgcagcatggcgcggcggcggc gccggtgagcgcgccgaccagcggctatcaggaatttgtgcatgcggtggaacagggcggcacccagg cgagcgcggtggtgggcctgggcccgccgggcgaagcgggctataaagcgtttagcagcctgctggcg agcagcgcggtgagcccggaaaaatgcggctttggcgcgagcagcggcgaagaaggctataaaccgtt tcaggatctgattccgggctgcccgggcgatccggcgccggtgccggtgccgctgtttacctttggcctgg atcgcgaaccgccgcgcagcccgcagagcagccatctgccgagcagcagcccggaacatctgggcct ggaaccgggcgaaaaagtggaagatatgccgaaaccgccgctgccgcaggaacaggcgaccgatccg ctggtggatagcctgggcagcggcattgtgtatagcgcgctgacctgccatctgtgcggccatctgaaaca gtgccatggccaggaagatggcggccagaccccggtgatggcgagcccgtgctgcggctgctgctgcg gcgatcgcagcagcccgccgaccaccccgctgcgcgcgccggatccgagcccgggcggcgtgccgc tggaagcgagcctgtgcccggcgagcctggcgccgagcggcattagcgaaaaaagcaaaagcagcag cagctttcatccggcgccgggcaacgcgcagagcagcagccagaccccgaaaattgtgaactttgtgag cgtgggcccgacctatatgcgcgtgagc **(SEQ ID NO: 156)**
IL-18	IL-18Rα	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgtattttggc aaactcgaaagtaagctgagcgtgattcggaatcttaacgatcaggtgttattcatcgatcaaggcaacaga ccactctttgaagatatgacagattcagactgtagggataatgcccctaggaccatctttattataagcatgta taaggactctcagccccgcggtatggcagtaacgattagcgttaagtgcgagaagatttctacactttcatg cgaaaacaaaatcatctccttcaaagagatgaaccctcccgataatatcaaagataccaagtcggacataat tttctttcagagatccgtcccaggacacgacaataagatgcaattcgaatccagcagttacgagggatacttt ctggcttgtgagaaggaacgtgacttgttcaaactgatcctgaagaaagaggacgagctaggggaccgat ctatcatgttcactgtgcagaacgaggactctggaggcggaagcgggggtggcggcagcggcggtgga ggatcaggtggcgggggtccgggggcggaagtctgcaggccgagagctgcactagccggccccata taactgtggtcgaaggggagccattctatctgaaacattgttcctgctcccttgcccatgaaattgaaaccac aaccaagagctggtacaaatctagtgggtctcaagagcacgtcgagttgaacccaagatcatctagtagga tcgccctgcatgactgcgttctagagttttggccggtggaattaaatgacaccggatcttacttcttccagatg aagaattacacccagaaatggaagctgaacgtgatacgacgcaacaagcactcatgcttcacagaacgtc aggtgacctcgaaaatcgtggaagtgaaaaagttctttcagattacatgcgagaacagttactatcaaacgc tagtgaatagcacgagcctgtacaaaaactgtaagaaacttctgctggagaacaataaaaaccctactatca aaaaaaatgcagaattcgaggatcagggctattacagttgtgtgcattttctccaccacaatggtaagctattc aatatcaccaagacgttcaacatcaccattgtggaggatcgctccaacatagtacctgtgttattgggtccta

		aacttaaccacgtggcagtggagctggggaaaaacgtgagactcaattgctcagccttgctgaacgaaga ggatgttatttattggatgtttggggaagaaaatggaagtgacccgaacattcacgaagagaaggagatgc gaatcatgacaccagaggggaaatggcacgcgagtaaggtcctcagaattgaaaatattggcgaatcaaa tctcaacgtcctctataactgtaccgtagcatccacaggcggcactgatactaagtcctttatccttgtgcgta aggccgatatggctgacatccccggccacgtattcacacggggaatgatcattgctgttctgatcctggtgg cagtagtgtgtttggttactgtatgtgttatctaccgcgtggacttagttctgttttataggcacctgacccgaag agacgaaacccttacagatggcaagacttatgacgcgttcgtgtcgtatcttaaagaatgccggcccgaga atggagaggagcacacgtttgctgtcgaaattctccccagagtcctggagaagcattttggttacaagctgt gcatcttcgaaagagacgtcgtgcccggtggcgccgtggtcgacgagatacattccctgatcgagaagtc ccgcaggttgatcatagtcctctcaaagtcttacatgagcaatgaggtgcggtacgaactcgagagcggac tgcatgaggctttagtcgagaggaagattaagattattttgatcgagtttacacctgtgactgactttaccttcct ccctcagtcactgaaactccttaagtctcacagggtactgaagtggaaagctgataaatccctctcttataata gccggttttggaagaacctattgtacctgatgccagccaaaacagtcaagcctggacgcgatgagcccga agttctgccagttctgagcgagtcc **(SEQ ID NO: 157)**
IL-18	IL-18Rβ	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgtattttggc aaactcgaaagtaagctgagcgtgattcggaatcttaacgatcaggtgttattcatcgatcaaggcaacaga ccactctttgaagatatgacagattcagactgtagggataatgcccctaggaccatctttattataagcatgta taaggactctcagccccgcggtatggcagtaacgattagcgttaagtgcgagaagatttctacactttcatg cgaaaacaaaatcatctccttcaaagagatgaaccctcccgataatatcaaagataccaagtcggacataat tttctttcagagatccgtcccaggacacgacaataagatgcaattcgaatccagcagttacgagggatacttt ctggcttgtgagaaggaacgtgacttgttcaaactgatcctgaagaaagaggacgagctaggggaccgat ctatcatgttcactgtgcagaacgaggactctggaggcggaagcgggggtggcggcagcggcggtgga ggatcaggtggcgggggtccgggggcggaagtctgcagtttaatatctctggatgcagtacgaagaaat tgctctggacatactctactaggagcgaggaagagttcgtgcttttctgcgatttaccagaaccacagaaatc ccatttttgtcacagaaatcgtctttctcctaagcaggttcccgaacacctgcccttcatgggctccaacgacc ttagtgacgttcaatggtaccagcaaccaagcaatggcgaccctctggaagacatacgcaagagttaccc ccatattatccaggataaatgcacgctacatttcctgaccccaggcgtcaacaacagtggatcttatatatgta ggcctaagatgatcaaatccccctacgacgtggcttgttgcgtcaagatgattctcgaggtgaagccccag accaatgcctcatgtgagtactccgcctctcacaaacaggaccttctgctggggtcgaccggcagtataag ctgcccatcgctctcttgtcagagtgatgcgcagagccctgctgtgacatggtacaaaaacggaaagctac tgtcagtggagcgctcaaaccgtattgtagtagacgaagtctacgactatcaccaaggcacctacgtgtgc gattatacacagtctgatacggtctccagttggactgtgcgggccgtggtgcaggtacggaccatcgtggg ggacacaaaactgaagcccgacatccttgatccagttgaggacaccctggaggtggagctcgggaagcc cctgactatctcctgtaaagcaagatttggcttcgagcgagtatttaaccctgttatcaagtggtatattaaaga tagcgatctcgagtgggaggtatcagtgcctgaagccaaatccatcaaatcaactctgaaggatgaaatca ttgagcgaaatattattcttgagaaggttacccagcgcgatctccgccgcaaatttgtctgcttcgtgcaaaa cagcataggcaatactactcagagcgtgcagctgaaagagaagcgtggtgtcgtcttgttgtacatcctgct cggaacaattggtacactcgtagccgtgttggccgcctcagccctgctctacaggcattggattgaaatcgt gttgctttacaggacatatcagagcaaggaccagactctgggcgacaaaaaggatttcgatgcattcgttag ctatgctaaatggtcttcatttcctagcgaagctacatcctccctgagcgaggaacacttagccttatcactgtt tccagatgtgttagaaaataaatatggctatagcctgtgtttgctggagcgcgacgttgcaccaggggggt gtatgctgaagacatcgtcagcatcatcaagcggtccaggaggggaatatttatattaagccctaactacgt caacggtccatcgattttcgaactgcaggctgcagtgaacttggcgctcgatgaccagacgctcaagctga ttctcatcaagttctgctactttcaagagcccgagtctcttcctcacctagtcaagaaggcgctgagagtcctg ccgaccgtgacatggcgaggactaaagtctgtgccgccgaattccagattctgggcaaagatgcggtatc atatgcccgttaaaaattcccaaggttttacttggaaccagctgcggattaccagtcggatcttccagtggaa

		ggggctgtctagaaccgagaccaccggaagatccagtcaacccaaagaatgg **(SEQ ID NO: 158)**

Table 11a – Amino Acid Sequences of Exemplary anti-HER2 Chimeric Antigen Receptor (CAR)

CD8a Signal Peptide	MALPVTALLLPLALLLHAARP **(SEQ ID NO: 174)**
HER2 scFv	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQ GTKVEIKRTGSTSGSGKPGSGEGSEVQLVESGGGLVQPGGSLRLSCAAS GFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDVWGQGTLVTVSS SG **(SEQ ID NO: 159)**
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD **(SEQ ID NO: 160)**
CD8a Transmembrane Domain	IYIWAPLAGTCGVLLLSLVITLYC **(SEQ ID NO: 161)**
CD3ζ Stimulatory Domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR **(SEQ ID NO: 162)**
Complete CAR	MALPVTALLLPLALLLHAARPDIQMTQSPSSLSASVGDRVTITCRASQDV NTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTPPTFGQGTKVEIKRTGSTSGSGKPGSGEGSEVQLV ESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGG DGFYAMDVWGQGTLVTVSSSGTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA LHMQALPPR **(SEQ ID NO: 163)**

Table 11b – DNA Sequences of Exemplary anti-HER2 Chimeric Antigen Receptor (CAR)

CD8a Signal Peptide	Atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccg **(SEQ ID NO: 164)**
HER2 scFv	Gacattcaaatgacacagagtccctcatccctcagtgccagcgtgggcgatcgggtgactataacctgcagagctt ctcaggacgtgaataccgctgtggcgtggtaccagcagaagccaggcaaagcgcctaagcttctcatttatagtgc cagcttcctgtactcaggtgttccgtctcgcttttctggaagtagaagtgggaccgatttcacattgacgatcagcagc ttgcagcccgaagatttcgccacctactactgtcagcagcactacactaccccaccgacatttggtcaaggcacaaa agtagagattaaacgcactggttccaccagcgggagcgggaaacccggctctggggaggggagcgaggtcca gctggtggaatccgggggtggtcttgtgcagccaggaggatccttgaggttgtcctgcgccgcaagcggctttaac atcaaagatacatacatccattgggtccgacaggcccctggaaagggcctggagtgggtcgcccggatctaccca

	actaacgggtacactcgctacgctgatagcgtcaagggtcggtttactatttctgccgacacctcaaaaaacacagc ctacctccagatgaactctctcagagctgaggatacagccgtgtactattgcagccggtggggaggcgacgggttc tacgctatggatgtgtgggggcagggcacactggtcaccgtgagctcatccgga **(SEQ ID NO: 165)**
CD8a Hinge	Accacgacgccagcgccgcgaccaccaacaccggcgcccaccatcgcgtcgcagcccctgtccctgcgccca gaggcgtgccggccagcggcgggggggcgcagtgcacacgagggggctggacttcgcctgtgat **(SEQ ID NO: 166)**
CD8a Transmembrane Domain	Atctacatctgggcgcccttggccgggacttgtggggtccttctcctgtcactggttatcacccttactgc **(SEQ ID NO: 167)**
CD3ζ Stimulatory Domain	Agagtgaagttcagcaggagcgcagacgcccccgcgtaccagcagggccagaaccagctctataacgagctc aatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggaaagc cgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtga gattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccacc aaggacacctacgacgcccttcacatgcaggccctgcccccctcgc **(SEQ ID NO: 168)**
Complete CAR	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccggacattcaaatga cacagagtccctcatccctcagtgccagcgtgggcgatcgggtgactataacctgcagagcttctcaggacgtgaa taccgctgtggcgtggtaccagcagaagccaggcaaagcgcctaagcttctcatttatagtgccagcttcctgtact caggtgttccgtctcgcttttctggaagtagaagtgggaccgatttcacattgacgatcagcagcttgcagcccgaa gatttcgccacctactactgtcagcagcactacactaccccaccgacatttggtcaaggcacaaaagtagagattaa acgcactggttccaccagcgggagcgggaaacccggctctggggaggggagcgaggtccagctggtggaatc cgggggtggtcttgtgcagccaggaggatccttgaggttgtcctgcgccgcaagcggctttaacatcaaagataca tacatccattgggtccgacaggcccctggaaagggcctggagtgggtcgcccggatctacccaactaacgggtac actcgctacgctgatagcgtcaagggtcggtttactatttctgccgacacctcaaaaaacacagcctacctccagatg aactctctcagagctgaggatacagccgtgtactattgcagccggtggggaggcgacgggttctacgctatggatg tgtgggggcagggcacactggtcaccgtgagctcatccggaaccacgacgccagcgccgcgaccaccaacacc ggcgcccaccatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgggggggcgcagt gcacacgagggggctggacttcgcctgtgatatctacatctgggcgcccttggccgggacttgtggggtccttctcc tgtcactggttatcacccttactgcagagtgaagttcagcaggagcgcagacgcccccgcgtaccagcagggcc agaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccggg accctgagatgggggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataa gatggcggaggcctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggccttta ccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggccctgcccccctcgc **(SEQ ID NO: 169)**

Table 12 – Amino Acid Sequences of Exemplary Chemokines

hCCL19	MALLLALSLLVLWTSPAPTLSGTNDAEDCCLSVTQKPIPGYIVRNF HYLLIKDGCRVPAVVFTTLRGRQLCAPPDQPWVERIIQRLQRTSAK MKRRSS **(SEQ ID NO: 178)**
hCXCL12	MNAKVVVVLVLVLTALCLSDGKPVSLSYRCPCRFFESHVARANVK HLKILNTPNCALQIVARLKNNNRQVCIDPKLKWIQEYLEKALNK **(SEQ ID NO: 179)**

EQUIVALENTS

[0316] It is to be appreciated by those skilled in the art that various alterations, modifications, and improvements to the present disclosure will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of the present disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawing are by way of example only and any invention described in the present disclosure if further described in detail by the claims that follow.

[0317] Those skilled in the art will appreciate typical standards of deviation or error attributable to values obtained in assays or other processes as described herein. The publications, websites and other reference materials referenced herein to describe the background of the invention and to provide additional detail regarding its practice are hereby incorporated by reference in their entireties.

CLAIMS

1. A modified immune cell comprising a fusion protein comprising a cytokine, a linker, and a cytokine receptor,

wherein the modified immune cell is a stem cell, macrophage, monocyte, or dendritic cell and

the cytokine binds the cytokine receptor.

2. The modified immune cell of claim 1, wherein the fusion protein is membrane-bound.

3. The modified immune cell of claim 1 or 2, wherein the linker is a flexible linker.

4. The modified immune cell of any one of claims 1-3, wherein the linker is a cleavable linker.

5. The modified immune cell of any one of claims 1-4, further comprising a chimeric antigen receptor (CAR).

6. The modified immune cell of any one of claims 1-5, wherein the fusion protein further comprises a signal peptide.

7. The modified immune cell of claim 6, wherein the fusion protein comprises, from N-terminus to C-terminus: the signal peptide, the cytokine, the linker, and the cytokine receptor.

8. The modified immune cell of any one of claims 1-7, wherein the fusion protein comprises an amino acid sequence at least 80% identical to a sequence selected from Table 2a, Table 2b, Table 3a, Table 3b, Table 6, Table 8, or Table 9.

9. A modified immune cell comprising one or more nucleic acids encoding a fusion protein comprising a cytokine, a linker, and a cytokine receptor,

wherein the modified immune cell is a stem cell, macrophage, monocyte or dendritic cell and

the cytokine binds the cytokine receptor.

10. The modified immune cell of claim 9, wherein the fusion protein is membrane-bound.

11. The modified immune cell of claim 9 or 10, wherein the linker is a flexible linker.

12. The modified immune cell of any one of claims 9-11, wherein the linker is a cleavable linker.

13. The modified immune cell of any one of claims 9-12, further comprising a chimeric antigen receptor (CAR).

14. The modified immune cell of claim 13, wherein the fusion protein further comprises a signal peptide.

15. The modified immune cell of claims 14, wherein the fusion protein comprises, from N-terminus to C-terminus: the signal peptide, the cytokine, the linker, and the cytokine receptor.

16. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 10.

17. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 11b.

18. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 4a, Table 4b, or Table 7.

19. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 5a or Table 5b.

20. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a signal peptide sequence selected from Table 8.

21. The modified immune cell of any one of claims 9-15, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a linker sequence selected from Table 8.

22. The modified immune cell of any one of claims 1-21, wherein the signal peptide is or comprises a CD8a, IgG κ, PDGFR-β, Type I Interferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2 signal peptide.

23. The modified immune cell of any one of claims 1-22, wherein the cytokine is or comprises a pro-inflammatory cytokine.

24. The modified immune cell of any one of claims 1-22, wherein the cytokine is or comprises an anti-inflammatory cytokine.

25. The modified immune cell of claim 23, wherein the cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ),

Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, or GM-CSF.

26. The modified immune cell of claim 24, wherein the cytokine is or comprises IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β.

27. The modified immune cell of any one of claims 1-22, wherein the cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, or TGF-β .

28. The modified immune cell of any one of claims 1-22, wherein the cytokine receptor is or comprises a pro-inflammatory cytokine receptor.

29. The modified immune cell of any one of claims 1-22, wherein the cytokine receptor is or comprises an anti-inflammatory cytokine receptor.

30. The modified immune cell of claim 28, wherein the cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, or CSF2-Rβ.

31. The modified immune cell of claim 29, wherein the cytokine receptor is or comprises IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2.

32. The modified immune cell of any one of claims 1-3a, wherein the cytokine receptor is or comprises IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2.

33. The modified immune cell of any one of claims 1-32, wherein the linker is or comprises a linker selected from a group consisting of: a $(G4S)_n$ linker, wherein n = 1-5 (SEQ ID NO: 170), a Whitlow linker, and Linker 26.

34. A modified immune cell comprising a fusion protein comprising interleukin 10 (IL-10), a linker, and interleukin-10 receptor (IL10R).

35. A modified immune cell comprising a fusion protein comprising interferon beta (IFNβ), a linker, and interferon-α/β receptor (IFNAR).

36. The modified immune cell of claim 34 or 35, wherein the fusion protein is membrane-bound.

37. The modified immune cell of claim 34 or 35, wherein the linker is a flexible linker.

38. The modified immune cell of any one of claims 34-37, wherein the linker is a cleavable linker.

39. The modified immune cell of any one of claims 34-38, further comprising a chimeric antigen receptor (CAR).

40. A pharmaceutical composition comprising a modified immune cell of any one of claims 1-39.

41. The pharmaceutical composition of claim 40, comprising a pharmaceutically acceptable carrier.

42. A nucleic acid construct comprising one or more nucleic acids encoding a fusion protein comprising a cytokine and a cytokine receptor.

43. The nucleic acid construct of claim 42, further comprising one or more nucleic acids encoding a chimeric antigen receptor (CAR).

44. A pharmaceutical composition comprising the nucleic acid construct of claim 42 or 43.

45. The pharmaceutical composition of claim 44, comprising a pharmaceutically acceptable carrier.

46. A method of treating or preventing a disease or disorder in a subject, comprising delivering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of claims 40, 41, 44, or 45.

47. A method of modifying an immune cell, the method comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding a fusion protein comprising a cytokine, a linker, and a cytokine receptor.

48. The method of claim 47, wherein the linker is a flexible linker.

49. The method of claim 47 or 48, wherein the linker is a cleavable linker.

50. The method of any one of claims 47-49, wherein the nucleic acid construct further comprises one or more nucleic acids encoding a chimeric antigen receptor (CAR).

51. The method of any one of claims 47-50, wherein the delivering comprises electroporation or transfection with DNA, mRNA, or chemically modified mRNA.

52. The method of any one of claims 47-50, wherein the delivering comprises transduction with an adeno-associated viral (AAV) vector, an adenoviral vector, or a retroviral vector.

53. The method of claim 52, wherein the retroviral vector comprises a lentiviral vector or a gammaretroviral vector.

54. The method of claim 53, wherein the lentiviral vector is packaged with a Vpx protein.

55. The method of claim 52, wherein the adenoviral vector comprises an Ad2 vector or an Ad5 vector.

56. The method of claim 55, wherein the Ad5 vector comprises an Ad5f35 adenoviral vector.

57. The method of any one of claims 47-50, wherein the delivery comprises transposon-based delivery or CRISPR-based targeted integration.

58. A modified immune cell comprising an exogenous cytokine and a chimeric antigen receptor (CAR),

wherein the modified immune cell is a stem cell, macrophage, monocyte, or dendritic cell and

the exogenous cytokine is or comprises a pro-inflammatory cytokine, an anti-inflammatory cytokine, or a chemoattractant chemokine.

59. The modified immune cell of claim 58, wherein the exogenous cytokine comprises a signal peptide.

60. The modified immune cell of claim 58 or 59, wherein the exogenous cytokine comprises an amino acid sequence at least 80% identical to a sequence selected from Table 2a, Table 2b, Table 6, or Table 8.

61. A modified immune cell comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR),

wherein the modified immune cell is a stem cell, macrophage, monocyte or dendritic cell and

the exogenous cytokine is or comprises a pro-inflammatory cytokine, an anti-inflammatory cytokine, or a chemoattractant chemokine.

62. The modified immune cell of claim 61, wherein the exogenous cytokine further comprises a signal peptide.

63. The modified immune cell of claim 61 or 62, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 4a, Table 4b, Table 7, or Table 11b.

64. The modified immune cell of claim 61 or 62, wherein the one or more nucleic acids comprise a sequence at least 80% identical to a sequence selected from Table 8.

65. The modified immune cell of any one of claims 61-64, wherein the one or more nucleic acids encode a signal peptide.

66. The modified immune cell of claim 62 or 65, wherein the signal peptide is or comprises a CD8a, IgG κ, PDGFR-β, Type I Interferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNLR1, TNFR1, TNFR2, IL-1R1, IL-1R3, IL-6Rα, gp130, IL-12Rβ1, IL-12Rβ2, IL-17RA, IL-17RB, IL-17RC, IL-23R, CSF2-Rα, CSF2-Rβ, IL-4Rα, IL-4Rα1, IL-2Rγc, IL-10R1, IL-10R2, IL-13Rα1, IL-18Rα, IL-18Rβ, CSF1-R, TGF-βR1, or TGF-βR2 signal peptide.

67. The modified immune cell of any one of claims 58-66, wherein the exogenous cytokine is or comprises a Type I Inteferon (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21, IFN-β, IFN-ω, IFN-ε, or IFN-κ), Type II Interferon (IFN-γ), Type III Interferon (IFN-λ1, IFN-λ2, IFN-λ3, or IFN-λ4), TNF-α, IL-1β, IL-6, IL-12, IL-17, IL-23, GM-CSF, IL-4, IL-10, IL-13, IL-18, M-CSF, TGF-β, CCL19, or CXCL12.

68. The modified immune cell of claim 67, wherein the exogenous cytokine is or comprises IFN-γ, IL-10, CCL19, or CXCL12.

69. A pharmaceutical composition comprising a modified immune cell of any one of claims 58-68.

70. The pharmaceutical composition of claim 69, comprising a pharmaceutically acceptable carrier.

71. A nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR).

72. A pharmaceutical composition comprising the nucleic acid construct of claim 71.

73. The pharmaceutical composition of claim 72, comprising a pharmaceutically acceptable carrier.

74. A method of treating or preventing a disease or disorder in a subject, comprising delivering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of claims 69, 70, 72, or 73.

75. A method of modifying an immune cell, the method comprising delivering to the immune cell a nucleic acid construct comprising one or more nucleic acids encoding an exogenous cytokine and a chimeric antigen receptor (CAR).

76. The method of claim 75, wherein the delivering comprises electroporation or transfection with DNA, mRNA, or chemically modified mRNA.

77. The method of claim 75, wherein the delivering comprises transduction with an adeno-associated viral (AAV) vector, an adenoviral vector, or a retroviral vector.

78. The method of claim 77, wherein the retroviral vector comprises a lentiviral vector or a gammaretroviral vector.

79. The method of claim 78, wherein the lentiviral vector is packaged with a Vpx protein.

80. The method of claim 77, wherein the adenoviral vector comprises an Ad2 vector or an Ad5 vector.

81. The method of claim 80, wherein the Ad5 vector comprises an Ad5f35 adenoviral vector.

82. The method of claim 50, wherein the delivery comprises transposon-based delivery or CRISPR-based targeted integration.