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(54) Title: IN VIVO DELIVERY TO IMMUNE CELLS

(57) Abstract: The present disclosure provides methods of producing a modified immune cell comprising a chimeric antigen receptor (CAR), the method including the step of administering to a subject a composition comprising (a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes the CAR, and (b) a delivery vehicle, wherein following administration of the composition one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising the CAR, in the subject, and wherein the modified immune cell comprising the CAR possesses targeted effector activity. Also provided herein are compositions including (a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes the CAR, and (b) a delivery vehicle, wherein the delivery vehicle comprises at least one targeting moiety.

IN VIVO DELIVERY TO IMMUNE CELLS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/287,725, filed December 9, 2021, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Although immunotherapies have been investigated for many diseases and disorders, including cancer, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), systemic amyloidosis, prion disease, cardiovascular disease, atherosclerosis, fibrosis, limitations that have been encountered still need to be addressed.

[0003] Therefore, a need exists for the development of therapeutic compositions targeted to immune cells.

SUMMARY OF THE INVENTION

[0004] Cellular therapies including ex vivo modification of immune cells have received significant attention from the scientific community for the past several years, including the first approvals of cell therapies for use in humans. While the power of ex vivo modified immune cells is apparent, there are several challenges with the creation, transport and administration of such modified cells. As such, the present disclosure encompasses the recognition that certain delivery vehicles are advantageous in facilitating the in vivo modification of immune cells to avoid issues with ex vivo modification and subsequent patient administration. The teachings provided herein allow for harnessing of the power of immune cells modified to target particular cells, tissue, or other undesired targets while avoiding many current problems.

[0005] The present disclosure encompasses, among other things, methods of modifying immune cells (e.g., stem cells, macrophages, monocytes, and/or dendritic cells) in a subject by

delivering compositions comprising one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes the CAR, and a delivery vehicle.

[0006] In one aspect, the present disclosure provides methods of producing a modified immune cell comprising a chimeric antigen receptor (CAR), the methods comprising administering to a subject a composition comprising (a) one or more nucleic acid molecules, wherein at least a portion of one or more nucleic acid molecules encodes a CAR, and (b) a delivery vehicle; wherein following administration of the composition one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising the CAR, wherein the immune cell is a stem cell, monocyte, macrophage, or dendritic cell in the subject, and wherein the modified immune cell comprising the CAR possesses targeted effector activity.

[0007] In another aspect, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, the methods comprising administering to a subject a therapeutically effective amount of a composition comprising (a) one or more nucleic acid molecules, wherein at least a portion of one or more nucleic acid molecules encodes a chimeric antigen receptor (CAR), and (b) a delivery vehicle; wherein following administration of the composition the one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising the CAR, wherein the immune cell is a stem cell, monocyte, macrophage, or dendritic cell in the subject, and wherein at least one sign or symptom of the disease or disorder is improved in the subject after administration.

[0008] In some embodiments, a composition is a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0009] In some embodiments, one or more nucleic acid molecules comprise DNA or messenger RNA (mRNA). In some embodiments, one or more nucleic acid molecules comprise a modification comprising a modified nucleotide, an alteration to the 5' untranslated region (UTR), an alteration to the 3' UTR, a cap structure, a poly(A) tail, or combinations thereof. In some embodiments, a cap structure comprises AGCap1, m6AGCap1, or Anti-Reverse Cap Analog (ARCA). In some embodiments, a modified nucleotide comprises pseudouridine (PsU),

5-methoxyuridine (5moU), 5-methylcytidine/pseudouridine (5meC PsU), N1-methyl-pseudouridine (N1mPsU), or combinations thereof.

[0010] In some embodiments, one or more nucleic acid molecules are purified nucleic acid molecules. In some embodiments, purified nucleic acid molecules are produced by a method comprising silica membrane purification, high performance liquid chromatography (HPLC), Dynabeads, LiCl precipitation, phenol-chloroform extraction, resin based purification, polyA isolation, RNeasy, or combinations thereof.

[0011] In some embodiments, one or more nucleic acid molecules are codon-optimized. In some embodiments, one or more nucleic acid molecules are codon-optimized for expression in a stem cell, monocyte, macrophage, or dendritic cell.

[0012] In some embodiments, a composition further comprises an additional payload. In some embodiments, an additional payload is or comprises a pathogen recognition receptor agonist, polyinosinic:polycytidylic acid (poly I:C), a TLR7/8 agonist, a CpG oligodeoxynucleotide, a NOD-like receptor (NLR) agonist, a RIG-I-like receptor (RLR) agonist, a C-type lectins receptor (CLR) agonist, a cytosolic DNA sensing, the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) agonist, an interferon-inducible protein 16 (IFI16) agonist, a DEAD-box helicase 41 (DDX41) agonist, an LRR binding FLII interacting protein 1 (LRRFIP1) agonist, an absent in melanoma 2 (AIM2) agonist, an aryl hydrocarbon receptor (AhR) ligand, or combinations thereof.

[0013] In some embodiments, one or more nucleic acid molecules and an additional payload are encapsulated within a delivery vehicle. In some embodiments, a delivery vehicle is or comprises a liposome, a lipid nanoparticle, a polymer, an adeno-associated viral (AAV) vector, an adenoviral vector, a retroviral vector or combinations thereof. In some embodiments, a liposome or lipid nanoparticle comprises one or more cationic lipids, one or more non-cationic lipids, one or more cholesterol-based lipids, one or more PEG-modified lipids, or combinations thereof. 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.

[0014] In some embodiments, a step of administering is or comprises transarterial, subcutaneous, intravenous, intradermal, intratumoral, intranodal, intramedullary, intramuscular, or intraperitoneal delivery.

[0015] In some embodiments, targeted effector activity directed against a target cell is or comprises phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion.

[0016] In some embodiments, at least a portion of one or more nucleic acid molecules encodes a peptide agent. In some embodiments, at least a portion of one or more nucleic acid molecules encodes a peptide agent that primes and/or polarizes the modified immune cell toward a pro-inflammatory phenotype. In some embodiments, a peptide agent is or comprises a cytokine, a cytokine receptor, a chemokine, a chemokine receptor, an immune ligand, a dominant negative receptor, a switch receptor, a secreted antibody or fragment thereof, a transcription factor, an angiopoietin receptor, or combinations thereof.

[0017] In some embodiments, following administration of the composition, one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising a cytokine, cytokine receptor, chemokine, chemokine receptor, immune ligand, dominant negative receptor, switch receptor, secreted antibody or fragment thereof, transcription factor, angiopoietin receptor, or combination thereof.

[0018] In some embodiments, a portion of one or more nucleic acid molecules encoding a CAR and a portion of one or more nucleic acid molecules encoding a peptide agent are present in a composition at a ratio of approximately 1000:1, 500:1, 250:1, 100:1, 50:1, 20:1, 10:1, 5:1, 2:1, 1:1, 1:2, 1:5, 1:10, 1:50, 1:100, 1:250, 1:500, or 1:1000.

[0019] In some embodiments, a portion of the one or more nucleic acid molecules encoding a CAR are present in a first delivery vehicle and a portion of one or more nucleic acid molecules encoding a peptide agent are present in a second delivery vehicle. In some embodiments, a first delivery vehicle is or comprises a first population of lipid nanoparticles or liposomes and a second delivery vehicle is or comprises a second population of lipid nanoparticles or liposomes.

[0020] In some embodiments, a portion of one or more nucleic acid molecules encoding a CAR and a portion of one or more nucleic acid molecules encoding a peptide agent are separated by a cleavage peptide.

[0021] In some embodiments, a composition is administered alone or in combination with one or more therapeutic agents, procedures, or modalities.

[0022] In some embodiments, an immune cell is mobilized prior to administering a composition to a subject. In some embodiments, an immune cell is mobilized by administering G-CSF, GM-CSF, FLT3-Ligand, or plerixafor to a subject.

[0023] In another aspect, the present disclosure provides a composition comprising (a) one or more nucleic acid molecules, wherein at least a portion of one or more nucleic acid molecules encodes a CAR, and (b) a delivery vehicle. In some embodiments, a delivery vehicle comprises at least one targeting moiety. In some embodiments, a targeting moiety facilitates passive targeting of a composition to a desired target. In some embodiments, a targeting moiety facilitates active targeting of a composition to a desired target. In some embodiments, a targeting moiety is or comprises an antibody or any fragment thereof. In some embodiments, an antibody or any fragment thereof binds to CD14, CD11b, CD163, CD206, CD33, CD209, or combinations thereof. In some embodiments, a targeting moiety is or comprises a small molecule. In some embodiments, a targeting moiety is or comprise a particular lipid or combination of hydrophobic entities.

BRIEF DESCRIPTION OF THE DRAWING

[0024] The drawings are for illustration purposes only, not for limitation.

[0025] **Figure 1** shows exemplary fusion proteins comprising IFN-β and IFNAR1/2 and IL10 and IL10RA/B.

[0026] **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.

[0027] **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.

[0028] **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.

DEFINITIONS

[0029] 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.

[0030] 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.

[0031] *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).

[0032] *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, gene expression changes, antigen processing and presentation, metabolic changes, and other functions.

[0033] *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.

[0034] *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.].

[0035] *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).

[0036] *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.

[0037] *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.

[0038] *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.

[0039] *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.

[0040] *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.

[0041] *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.

[0042] *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.

[0043] *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.

[0044] *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.

[0045] *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.

[0046] *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.

[0047] *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.

[0048] *Cytotoxic:* As used herein, the term "cytotoxic" or "cytotoxicity" refers to killing or damaging cells. In some embodiments, cytotoxicity of the modified cells is improved, e.g. increased cytolytic activity of macrophages.

[0049] *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.

[0050] *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.

[0051] *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.

[0052] *Endogenous:* As used herein "endogenous" refers to any material from or produced inside a particular organism, cell, tissue or system.

[0053] *Exogenous:* As used herein, the term "exogenous" refers to any material introduced from or produced outside a particular organism, cell, tissue or system.

[0054] *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 some embodiments, expansion may occur *in vivo*.

[0055] *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.

[0056] *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).

[0057] *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.

[0058] *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.

[0059] *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.

[0060] *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.

[0061] *Immune cell*: As used herein, the term "immune cell," refers to a cell that is involved in an immune response, e.g., promotion or suppression 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 and stem cells capable of differentiating into one or more of these cell types. A source of immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) can be obtained from a subject.

[0062] *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.

[0063] *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.

[0064] *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.

[0065] *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.

[0066] *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.

[0067] ***Moiety***: Those skilled in the art will appreciate that a "moiety" is a defined chemical group or entity with a particular structure and/or or activity (e.g., targeting of a modified immune cell to a desired target), as described herein.

[0068] *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.

[0069] *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.

[0070] *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.

[0071] *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.

[0072] *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.

[0073] *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.

[0074] *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.

[0075] *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.

[0076] *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.

[0077] *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.

[0078] *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.

[0079] *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*.

[0080] *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.

[0081] *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.

[0082] *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.

[0083] *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.

[0084] *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.

[0085] *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.

[0086] *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.

[0087] *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.

[0088] 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

[0089] The present disclosure provides, *inter alia*, methods and compositions to facilitate the in vivo modification of immune cells (e.g., stem cells, monocytes, macrophages, and/or dendritic cells) in a subject. In some embodiments, modified immune cells are produced via use of one or more delivery vehicles, which may include one or more targeting moieties thereon.

Methods of In Vivo Immune Cell Modification

[0090] The present disclosure provides, among other things, methods of producing a modified immune cell (e.g., a stem cell, monocyte, macrophage, or dendritic cell) in a subject comprising administering to a subject a composition as described herein comprising: (a) one or more nucleic acid molecules, wherein at least a portion of one or more nucleic acid molecules encodes a chimeric antigen receptor (CAR), fusion protein and/or peptide agent, and (b) a delivery vehicle. Accordingly, in some embodiments, following administration of the composition one or more nucleic acid molecules are translated in an immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) to produce a modified immune cell comprising the

CAR, fusion protein and/or peptide agent. In some embodiments, the modified immune cell comprising the CAR, fusion protein and/or peptide agent possesses targeted effector activity.

[0091] The present disclosure also provides, among other things, methods of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition as described herein comprising: (a) one or more nucleic acid molecules, wherein at least a portion of one or more nucleic acid molecules encodes a CAR, fusion protein and/or peptide agent, and (b) a delivery vehicle. Accordingly, in some embodiments, following administration of the composition, one or more nucleic acid molecules are translated in an immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) to produce a modified immune cell comprising the CAR, fusion protein, and/or peptide agent. In some embodiments, at least one sign or symptom of the disease or disorder is improved in the subject after administration of a composition as described herein.

Delivery Vehicles

[0092] One or more nucleic acid molecules comprising one or more nucleic acid sequences encoding at least one CAR and/or peptide agent 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 (each a "delivery vehicle" as used herein). 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, lipofection, particle bombardment, or combinations thereof. One or more nucleic acid molecules can also be introduced into immune cells using mRNA transfection, e.g., cationic liposome-mediated transfection, lipofection, polymer encapsulation, or 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).

[0093] Biological methods for introducing one or more nucleic acid molecules 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)).

[0094] 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 (e.g., lipid nanoparticles), liposomes, and lipofectamine-nucleic acid complexes).

[0095] An exemplary class of delivery vehicles for delivery of a nucleic acid construct as described herein is a lipid-based system. One or more nucleic acid molecules 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, attached to a lipid nanoparticle (LNP) via a

linking molecule, entrapped in a liposome, entrapped in an LNP, complexed with a liposome, complexed with an LNP, 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°C. In some embodiments, a lipid-based system may comprise one or more lipids that facilitate targeting of the composition to a desired cell type or cell types (e.g., stem cells, monocytes, macrophages, or dendritic cells). In some embodiments, a delivery vehicle allows a composition to be preferentially taken up (e.g. endocytosed, phagocytosed) by an immune cell (e.g., stem cell, monocyte, macrophage, or dendritic cell) relative to a composition that does not comprise the delivery vehicle.

Targeting moieties

[0096] In some embodiments, a delivery vehicle may comprise one or more targeting moieties. In some embodiments, a targeting moiety may facilitate passive targeting of a composition to a desired target. In some embodiments, a targeting moiety may facilitate active targeting of a composition to a desired target.

[0097] In some embodiments, a targeting moiety may be or comprise one of more of an antibody (e.g., 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, an aptamer, a darpin, a centyrin, a naturally occurring or synthetic receptor, an affibody, or other engineered protein recognition molecule, for example, to bind to one or more of CD14, CD11b, CD163, CD206, CD33, CD209. In some embodiments, a targeting moiety may be or comprise a small molecule.

[0098] In some embodiments, a targeting moiety may be or comprise a particular lipid or combination of hydrophobic entities, for example, present in or forming an exterior surface of a liposome or lipid nanoparticle (e.g., for targeting to a particular cell type or cell types).

Nucleic acid molecules

[0099] In some embodiments of the present disclosure, one or more nucleic acid molecules are or comprise 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.

[0100] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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.

[0101] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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).

[0102] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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.

[0103] 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.

[0104] Thus, in some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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).

[0105] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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 (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 (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.

[0106] In some embodiments, mRNAs of the present disclosure (e.g., mRNAs encoding CARs, fusion proteins, and/or peptide agents) 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.

[0107] 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.

Administration of Additional Payloads

[0108] In some embodiments, methods of the present disclosure comprise one or more steps of administering to a subject an additional payload for modulating an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) during the process of modifying the immune cell. In some embodiments, a composition may comprise one or more additional payloads. In some embodiments, a composition may comprise one or more additional payloads in the same delivery vehicle as one or more nucleic acid molecules. In some embodiments, a composition may comprise one or more additional payloads in a different delivery vehicle than the one used with one or more nucleic acid molecules.

[0109] In some embodiments, an additional payload may be or comprise 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.

[0110] 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.

[0111] In some embodiments, administering to a subject an RNaseL inhibitor increases mRNA stability in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) relative to mRNA stability in a modified immune cell of the same type in a subject that that was not administered an RNaseL inhibitor. In some embodiments, administering to a subject an RNaseL inhibitor increases CAR expression in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) relative to CAR expression in a modified immune cell of the same type in a subject that was not administered an RNaseL inhibitor. In some embodiments, administering to a subject an RNaseL inhibitor increases effector activity in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) relative to effector activity in a modified immune cell of the same type in a subject that was not administered an RNaseL inhibitor.

[0112] In some embodiments of the present disclosure, a step of administering an additional payload to a subject occurs before a step of administering a composition comprising an mRNA to the subject.

[0113] In some embodiments, methods of the present disclosure comprise a step of administering to a subject 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 combinations thereof. In some embodiments, a cytokine comprises IFN-β.

[0114] In some embodiments of the present disclosure, a step of administering to a subject a cytokine or immune stimulating recombinant protein occurs after a step of administering a composition comprising an mRNA to the subject.

[0115] In some embodiments, administering to a subject a cytokine or immune stimulating recombinant protein increases the viability of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) in the subject relative to a modified immune cell of the same type in a subject that was not administered the cytokine or immune stimulating recombinant protein. In some embodiments, administering to a subject a cytokine or immune stimulating recombinant protein increases protein (e.g., CARs, fusion proteins, and/or peptide agents) expression of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) in the subject relative to a modified immune cell of the same type in a subject that was not administered the cytokine or immune stimulating recombinant protein. In some embodiments, administering to a subject a cytokine or immune stimulating recombinant protein increases longevity of protein (e.g., CAR, fusion protein, and/or peptide agent) expression in a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) in the subject relative to a modified immune cell of the same type in a subject that was not administered the cytokine or immune stimulating recombinant protein. In some embodiments, administering to a subject a cytokine or immune stimulating recombinant protein increases effector activity of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) in the subject relative to a modified immune cell of the same type in a subject that was not administered the cytokine or immune stimulating recombinant protein. In some embodiments, administering to a subject a cytokine or immune stimulating recombinant protein increases pro-inflammatory (M1) polarization of a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) in the subject relative to a modified immune cell of the same type in a subject that was not administered the cytokine or immune stimulating recombinant protein.

Assays

[0116] A variety of assays may be performed to confirm the presence of one or more nucleic acid molecules as described herein in an immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) taken from a subject. 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.

[0117] 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., CAR, fusion protein, and/or peptide agent) expression, protein (e.g., CAR, fusion protein, and/or peptide agent) 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.

Methods of Treatment

[0118] 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 as described herein. 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.

[0119] 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). Pharmaceutical compositions as described herein can be administered to a subject in accordance with a dosage regimen described herein or as a physician may decide is advantageous using sound medical judgment, alone or in combination with one or more therapeutic agents, procedures, or modalities.

[0120] Pharmaceutical compositions as described herein 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 combinations of thereof.

[0121] 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 as described herein 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).

[0122] 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).

[0123] 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.

[0124] 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.

[0125] Pharmaceutical compositions as described herein 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.

[0126] 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.

[0127] 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 composition 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.

Compositions

[0128] The present disclosure provides, among other things, compositions comprising one or more nucleic acid molecules and a delivery vehicle (e.g., a delivery vehicle modified with one or more targeting moieties). In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a CAR, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a fusion protein, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a CAR and wherein at least a portion of the one or more nucleic acid molecules encodes a fusion protein, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a CAR and wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules wherein at least a portion of the one or more nucleic acid molecules encodes a fusion protein and wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent, and a delivery vehicle. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes a CAR wherein at least a portion of the one or

more nucleic acid molecules encodes a fusion protein and wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent, and a delivery vehicle.

[0129] In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes a CAR, a fusion protein, and/or a peptide agent, and wherein the portions of the one or more nucleic acid molecules encoding the CAR, the fusion protein, and/or the peptide agent are all present in a single nucleic acid molecule. In some embodiments, compositions of the present disclosure comprise one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes a CAR, a fusion protein, and/or a peptide agent, and wherein the portions of the one or more nucleic acid molecules encoding the CAR, the fusion protein, and/or the peptide agent are present in separate nucleic acid molecules.

[0130] In some embodiments, a delivery vehicle comprises or is a liposome, a lipid nanoparticle, a polymer, an adeno-associated viral (AAV) vector, an adenoviral vector, a retroviral vector or combinations thereof. In some embodiments, a liposome or lipid nanoparticle comprises one or more cationic lipids, one or more non-cationic lipids, one or more cholesterol-based lipids, one or more PEG-modified lipids, or combinations thereof. 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.

[0131] In some embodiments, compositions of the present disclosure comprise an additional payload. In some embodiments, an additional payload comprises or is a pathogen recognition receptor agonist (e.g., a TLR ligand (e.g., TLR1, 2, 3, 4, 5, 6, 7, 8, 9, or 13); polyinosinic:polycytidylic acid (poly I:C); a TLR7/8 agonist (e.g., a single stranded RNA that activates TLR7/8 or TLR7/8 agonists that are base analogs); a CpG oligodeoxynucleotide (ODN) (e.g., Class A, B, or C CpG ODNs); a NOD-like receptor (NLR) agonist (e.g., a NOD1, NOD2, or NOD1/2 agonist); a RIG-I-like receptor (RLR) agonist (e.g., a RIG-I agonist, an MDA-5 agonist, double stranded RNA, 5'triphosphate hairpin RNA, 5' triphosphate dsRNA, or Poly(dA:dT)); a C-type lectins receptor (CLR) agonist (e.g., a Dectin-1 agonist, a Mincle

agonist, a DC-SIGN agonist, a Dectin-2 agonist, beta glucan, curdlan, HKCA, laminarin, pustulan, scleroglucan, WGP, zymosan, furfurman, b-GlcCer, GlcC14C18, HKMT, TDB, TDB-HS15, or TDM); a cytosolic DNA sensing, the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) agonist; an interferon-inducible protein 16 (IFI16) agonist; a DEAD-box helicase 41 (DDX41) agonist; an LRR binding FLII interacting protein 1 (LRRFIP1) agonist; an absent in melanoma 2 (AIM2) agonist (e.g., dsDNA-EC, G3-YSD, HSV-60, ISd, ODN TTAGGG, PolydA:dT, VACV70, diABZI, 2'3'-cGAMP, 3'3'cGAMP, c-di-AMP, c-di-GMP, cAIMP, 2'2'cGAMP, 2'3'cGAM(PS)2(Rp/Sp), c-di-AMP fluorinated, 2'3'-c-di-AMP, 2'3'c-di-AM(PS)2(Rp,Rp)VacciGrade, c-diGMP fluorinated, 2'3'-c-diGMP, or DMXAA); an aryl hydrocarbon receptor (AhR) ligand; or combinations thereof.

[0132] In some embodiments, one or more nucleic acid molecules and the additional payload are encapsulated within the delivery vehicle. In some embodiments, one or more nucleic acid molecules and the additional payload are encapsulated within same the delivery vehicle. In some embodiments, one or more nucleic acid molecules and the additional payload are encapsulated within separate delivery vehicles.

Nucleic Acid Molecules

[0133] The present disclosure, among other things, provides nucleic acid molecules encoding at least one CAR, fusion protein, and/or peptide agent, or a fragment thereof described herein. In some embodiments, the present disclosure provides nucleic acid molecules encoding at least one CAR described herein or a fragment thereof. In some embodiments, the present disclosure provides 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 peptide agent described herein or a fragment thereof. An immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) can comprise one or more nucleic acid molecules (e.g., one or more exogenous nucleic acid molecules) encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) described herein.

[0134] 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.

[0135] Nucleic acid molecules encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) described herein, or a fragment thereof, can be a DNA molecule, an RNA molecule, or combinations thereof. In some embodiments, a nucleic acid molecule comprises or is a messenger RNA (mRNA) transcript encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) 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., a CAR, fusion protein or peptide agent) described herein or a fragment thereof.

[0136] In some embodiments including nucleic acid molecules encoding a CAR and a peptide agent, the portion of the one or more nucleic acid molecules encoding a CAR and the portion of the one or more nucleic acid molecules encoding a peptide agent may be present in the composition at a ratio of approximately 1000:1, 500:1, 250:1, 100:1, 50:1, 20:1, 10:1, 5:1, 2:1, 1:1, 1:2, 1:5, 1:10, 1:50, 1:100, 1:250, 1:500, or 1:1000.

[0137] In some embodiments, nucleic acid molecules encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) described herein or a fragment thereof comprise a modification. In some embodiments, a modification comprises a modified nucleotide, an alteration to the 5' untranslated region (UTR), an alteration to the 3' UTR, a cap structure, a poly(A) tail, or combinations thereof. In some embodiments, a cap structure comprises

AGCap1, m6AGCap1, or Anti-Reverse Cap Analog (ARCA). In some embodiments, a modified nucleotide comprises pseudouridine (PsU), 5-methoxyuridine (5moU), 5-methylcytidine/pseudouridine (5meC PsU), N1-methyl-pseudouridine (N1mPsU), or combinations thereof.

[0138] In some embodiments, nucleic acid molecules encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) described herein or a fragment thereof are purified nucleic acid molecules. In some embodiments, purified nucleic acid molecules are produced by a method comprising silica membrane purification, high performance liquid chromatography (HPLC), Dynabeads, LiCl precipitation, phenol-chloroform extraction, resin based purification, polyA isolation, RNeasy, or combinations thereof. In some embodiments, purified nucleic acid molecules are produced by a standard method of mRNA purification known in the art.

[0139] In some embodiments, all or a fragment of a protein (e.g., a CAR, fusion protein or peptide agent) described herein is encoded by a codon-optimized nucleic acid molecule, e.g., for expression in a cell (e.g., a mammalian cell). In some embodiments, one or more nucleic acid molecules of the present disclosure are codon-optimized for expression in a stem cell, monocyte, macrophage, or dendritic 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.

[0140] Expression of nucleic acids as described herein may be achieved by operably linking a nucleic acid encoding a protein (e.g., a CAR, fusion protein or peptide agent) 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.

[0141] In some embodiments, a vector comprising a nucleic acid molecule encoding at least one protein (e.g., a CAR, fusion protein or peptide agent) or fragment thereof as described herein 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).

[0142] 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).

[0143] 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.

[0144] 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 at least one protein (e.g.,

a CAR, fusion protein or peptide agent) or fragment thereof described herein. In some embodiments, an AAV serotype has a tropism for a particular tissue.

[0145] 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).

[0146] 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.

[0147] In some embodiments, a composition of the present disclosure comprises two or more nucleic acid sequences encoding proteins, e.g., a CAR, fusion protein and/or peptide agent. In some embodiments, a vector comprises two or more nucleic acid sequences encoding proteins, e.g., a CAR, fusion protein and/or peptide agent. In some embodiments, two or more nucleic acid sequences encoding proteins (e.g., a CAR, fusion protein and/or peptide agent) 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., a CAR, fusion protein and/or peptide agent) 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.

[0148] In some embodiments, a vector comprises at least one nucleic acid sequence encoding a protein (e.g., a CAR, fusion protein and/or peptide agent) 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

[0149] The present disclosure, among other things, provides pharmaceutical compositions comprising compositions as described herein (e.g., one or more nucleic acid molecules and a delivery vehicle) in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents, or excipients.

[0150] 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 as described herein can be determined by a physician with consideration of individual differences in age, weight, immune response, and condition of the patient (subject).

[0151] Pharmaceutical compositions described herein 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).

[0152] 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.

[0153] 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 intravenous, subcutaneous, intradermal, intratumoral, intranodal, intramedullary, intramuscular, transarterial, or intraperitoneal administration.

[0154] 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).

[0155] 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.

[0156] 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.

[0157] In some embodiments, pharmaceutical compositions described herein 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). In some embodiments, a second therapy can include a treatment that mobilizes immune cells of the present disclosure (e.g., G-CSF, GM-CSF, FLT3-Ligand, or plerixafor).

[0158] In some embodiments, pharmaceutical compositions described herein 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 described herein. Pharmaceutical compositions described herein may be administered before or following surgery.

[0159] 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).

Chimeric Antigen Receptors (CARs)

[0160] 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. 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.

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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]).

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] In some embodiments, an immune cell described herein (e.g., comprising or expressing a CAR, fusion protein, and/or a peptide agent 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 a fusion protein and/or a CAR described herein) comprises a dominant negative receptor, e.g., blocking an inhibitory checkpoint.

[0170] In some embodiments, a CAR described herein further comprises a cleavage peptide (e.g., a P2A, F2A, E2A and/or T2A peptide) and a second CAR comprising at least one inhibitory domain of anti-phagocytic signaling. In some embodiments, a 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, a 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, a 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).

[0171] In some embodiments, an immune cell described herein (e.g., comprising or expressing a CAR, fusion protein, and/or peptide agent 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

[0172] The present disclosure provides chimeric antigen receptors (CARs) 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

[0173] 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

[0174] 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

[0175] 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

[0176] 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.

[0177] 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; CD2; CD5; CD7; CD147; 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); immunoglobulin lambda-like polypeptide 1 (IGLL1); delta-like ligand 3 (DLL3); delta-like canonical notch ligand 4 (DLL4); TROP2; cMET; alpha fetoprotein (AFP); AXL; roundabout homolog 1 (ROBO1); CS1; or aspartate Beta-Hydroxylase (ASPH). 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.

[0178] 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)).

[0179] 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).

[0180] 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.

[0181] 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

[0182] 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. In some embodiments, a hinge domain is or comprises a CD8a or CD28 domain.

Transmembrane Domains

[0183] 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. In some embodiments, a transmembrane domain is or comprises a CD8a or CD28 domain.

FcR Transmembrane Domains

[0184] 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

[0185] 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

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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

[0190] 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

[0191] 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

[0192] 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).

[0193] 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, ICOSL intracellular signaling domain), FLT3, other intracellular signaling domains described herein, any derivative, variant, or fragment thereof, any synthetic sequence of a intracellular signaling domain that has the same functional capability, and any combinations thereof.

[0194] 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, FLT3, CD40, or any derivative, variant, or fragment thereof together with any of the signaling domains listed in the above paragraph in any combination.

Co-stimulatory Domains

[0195] 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.

[0196] 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).

[0197] 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

[0198] 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 that facilitates the initiation of translation.

Peptide Agents

[0199] In some embodiments, at least a portion of one or more nucleic acid molecules of the present disclosure encodes a peptide agent. In some embodiments, a peptide agent refers to a protein or peptide co-expressed with a CAR in an immune cell. In some embodiments, a peptide agent primes and/or polarizes a modified immune cell of the present disclosure toward a pro-inflammatory phenotype. 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.

[0200] 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 or is a cytokine (e.g., IFNα, IFNβ, IFNγ, GM-CSF, M-CSF, IFNλ, TNFα, IL-1b, IL-2, IL-6, IL-7, IL-8, IL-12, IL-15, IL-18, or IL-33); a cytokine receptor; a chemokine; a chemokine receptor (e.g., CCR2); an immune ligand (e.g., CD40L, 41BBL, OX40L, CD80, CD86, FLT3 ligand, or CLEC9A); a dominant negative receptor (e.g., dominant negative SIRPa); a switch receptor, a secreted antibody or fragment thereof (e.g., an anti-PD1 antibody, an anti-PDL1 antibody, an anti-CD47 antibody or an anti-SIRPα antibody); a transcription factor; an angiopoietin receptor (e.g., Tie2); or combinations thereof. In some embodiments a cytokine receptor is a constitutively active cytokine receptor (e.g., constitutively active GMCSF-R, MCSF-R, or IFNbR). In some embodiments a transcription factor activates an immune cell of the present disclosure to an M1 phenotype. In some embodiments, a peptide agent comprises or is dominant negative SIRPα, dominant negative PD1, dominant negative CD45, dominant negative SIGLEC 10, dominant negative LILRB, or combinations thereof. In some embodiments, a peptide agent comprises DNGR1.

Fc Receptors (FcR)

[0201] 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)

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.

Fusion Proteins

[0202] 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.

[0203] 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.

[0204] 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**).

[0205] 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.

[0206] 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 CAR 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 CAR-inducible promoter and cytosolic domain that associates in a drug-dependent manner, thus requiring CAR 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 CAR 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.

[0207] 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

[0208] In some embodiments, a fusion protein of the present disclosure comprises interleukin 10 (IL-10), a linker, and interleukin-10 receptor (IL10R).

[0209] In some embodiments, a fusion protein of the present disclosure comprises interferon beta (IFNβ), a linker, and interferon-α/β receptor (IFNAR).

[0210] 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.

[0211] 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.

[0212] 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).

[0213] 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.

[0214] 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**.

[0215] 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**.

[0216] 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.

[0217] 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.

[0218] 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).

[0219] 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).

[0220] 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.

[0221] 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.

[0222] 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

[0223] 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**.

[0224] 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.

[0225] 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.

[0226] 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.

[0227] 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.

[0228] 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**.

[0229] 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

[0230] 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).

[0231] In some embodiments, a linker is or comprises a linker selected from a group consisting of: a $(G4S)_n$ linker (wherein n = 1-5), a Whitlow linker, and Linker 26.

[0232] 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**.

[0233] 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

[0234] 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.

[0235] 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.

[0236] 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.

[0237] 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**.

[0238] 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

[0239] 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.

[0240] 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**.

[0241] 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**.

Target Immune Cells

[0242] The present disclosure provides, among other things, immune cells in a subject that can be modified according to the methods described herein.

[0243] The present disclosure, among other things, provides modified immune cells (e.g., stem cells, macrophages, monocytes, or dendritic cells) in a subject, wherein the subject is administered a composition as described herein comprising: (a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent, and (b) a delivery vehicle. Accordingly, in some embodiments, following administration of the composition the one or more nucleic acid molecules are translated in an immune cell (e.g., stem cell, macrophage, monocyte, or dendritic cell) to produce a modified immune cell comprising the CAR, fusion protein, and/or peptide agent. In some embodiments, the modified immune cell comprising the CAR, fusion protein, and/or peptide agent possesses targeted effector activity.

[0244] 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).

[0245] In some embodiments, a population of immune cells as described herein comprises stem cells, monocytes, macrophages, and/or dendritic cells.

[0246] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased viability relative to a modified immune cell of the same type comprising one or more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0247] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased expression of the one or more nucleic acid molecules encoding the CAR, fusion protein, and/or peptide agent provided herein relative to a modified immune cell of the same type comprising one or more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0248] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased CAR, fusion protein, and/or peptide agent expression relative to a modified immune cell of the same type comprising one or

more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0249] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased longevity of the one or more nucleic acid molecules encoding the CAR, fusion protein, and/or peptide agent provided herein relative to a modified immune cell of the same type comprising one or more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0250] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased longevity of the CAR, fusion protein, and/or peptide agent relative to a modified immune cell of the same type comprising one or more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0251] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased effector activity relative to a modified immune cell of the same type comprising one or more unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0252] In some embodiments, a modified immune cell (e.g., a stem cell, macrophage, monocyte, or dendritic cell) comprising one or more modified nucleic acid molecules, wherein at least a portion of the one or more modified nucleic acid molecules encodes a CAR, fusion protein, and/or peptide agent provided herein exhibits increased pro-inflammatory (M1) polarization relative to a modified immune cell of the same type comprising one or more

unmodified nucleic acid molecules, wherein at least a portion of the one or more unmodified nucleic acid molecules encodes the CAR, fusion protein, and/or peptide agent.

[0253] 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.

[0254] In some embodiments, immune cells in a subject (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein are treated with a pro-inflammatory agent. In some embodiments, immune cells in a subject (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein are administered a composition as described herein in combination with treatment with a pro-inflammatory agent. In some embodiments, compositions of the present disclosure are administered to a subject substantially simultaneously, before, or after treatment 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).

[0255] In some embodiments, immune cells in a subject (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein are treated with an anti-inflammatory agent. In

some embodiments, immune cells in a subject (e.g., stem cells, macrophages, monocytes, or dendritic cells) as described herein are administered a composition as described herein in combination with treatment with a pro-inflammatory agent. In some embodiments, compositions of the present disclosure are administered to a subject substantially simultaneously, before, or after treatment with an anti-inflammatory agent. 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.

Macrophages

[0256] 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.

[0257] 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.

[0258] 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.

[0259] 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.

[0260] 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).

[0261] In some embodiments, a modified macrophage in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein stimulates an immune response and/or inflammation, e.g., relative to a macrophage in a subject that has not been administered a composition described herein.

[0262] In some embodiments, a macrophage comprises or is an 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 modified macrophage in a subject that has been administered a composition described herein decreases an immune response in the subject. In some embodiments, a macrophage expresses one or more markers of M2 macrophages (e.g., one, two, or three of CD206, CD163, or CD209). In some embodiments, a modified macrophage in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein.

[0263] In some embodiments, a modified macrophage in a subject that has been administered a composition described herein comprises at least one upregulated pro-inflammatory (M1) marker and/or at least one downregulated anti-inflammatory (M2) marker as compared to a macrophage in a subject that has not been administered a composition described herein and/or the same macrophage in the subject before administration of a composition 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 modified macrophage. In some embodiments, at least one anti-inflammatory (M2) marker (e.g., CD206, CD163, and/or CD209) is downregulated in a modified macrophage.

[0264] In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits increased phagocytosis, e.g., relative to a macrophage in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits increased cytotoxicity against a tumor cell, e.g., relative to a macrophage in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits increased tumor antigen presentation (e.g., post-phagocytosis presentation) and/or increased antigen processing, e.g., relative to a in a subject that has not been

administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein.

[0265] In some embodiments, a modified macrophage in a subject that has been administered a composition 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, IL10, and/or IL4), e.g., relative to a macrophage in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits increased production of ROS, e.g., relative to a in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits induction of cell survival mechanisms, e.g., relative to a macrophage in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits induction of cell death mechanisms, e.g., relative to a macrophage in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified macrophage in a subject that has been administered a composition described herein exhibits one, two, three, or four of improved duration of CAR, fusion protein, and/or peptide agent, improved stability of the CAR, fusion protein, and/or peptide agenton the cell surface, increased level of CAR, fusion protein, and/or peptide agent, and/or decreased background activity of the CAR, fusion protein, and/or peptide agent, e.g., relative to a macrophage in a subject that has not been administered a composition described herein.

[0266] In some embodiments, a modified macrophage in a subject that has been administered a composition described herein decreases one or more signs and/or symptoms of an infection (e.g., of an infectious agent) in the subject, e.g., relative to a macrophage in a subject that has not been administered a composition 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 combinations 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.

[0267] In some embodiments, a modified macrophage in a subject that has been administered a composition described herein decreases formation and/or degrades existing aggregates via phagocytosis of at least one protein aggregate in the subject (e.g., the subject having a neurodegenerative disease, an inflammatory disease, a cardiovascular disease, a fibrotic disease, amyloidosis, or combinations thereof), e.g., relative to a macrophage in a subject that has not been administered a composition 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

[0268] 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.

[0269] 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.

[0270] 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.

[0271] In some embodiments, a modified monocyte in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits increased phagocytosis, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits enhanced survival, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits enhanced differentiation into macrophages (e.g., M1 or M2 macrophages), e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits increased cytotoxicity against a tumor cell, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits increased tumor antigen presentation (e.g.,

post-phagocytosis presentation) and/or increased antigen processing, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein.

[0272] In some embodiments, a modified monocyte in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits increased production of ROS, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits metabolic reprogramming, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits induction of cell survival mechanisms, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits induction of cell death mechanisms, e.g., relative to a monocyte in a subject that has not been administered a composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition 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 in a subject that has not been administered a

composition described herein. In some embodiments, a modified monocyte in a subject that has been administered a composition described herein exhibits one, two, three, or four of improved duration of CAR, fusion protein, and/or peptide agentexpression, improved stability of the CAR, fusion protein, and/or peptide agenton the cell surface, increased level of CAR, fusion protein, and/or peptide agent expression, or decreased background activity of the CAR, fusion protein, and/or peptide agent, e.g., relative to a monocyte in a subject that has not been administered a composition described herein.

Dendritic Cells

[0273] 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.

[0274] 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.

[0275] 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.

[0276] Without wishing to be bound by theory, it is believed that modification of a DC cell in a subject that has been administered a composition described herein can allow mature DCs to simultaneously exhibit increased antigen capture ability and T cell stimulation, e.g., relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein mediates tumor antigen presentation, e.g., increased tumor antigen presentation

relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein mediates tumor T cell stimulation, e.g., increased T cell stimulation relative to a DC in a subject that has not been administered a composition described herein.

[0277] In some embodiments, a modified DC in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits increased phagocytosis, e.g., relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein.

[0278] In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits one or both of increased expression of favorable genes or decreased expression of unfavorable genes, e.g., relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits increased production of ROS, e.g., relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits metabolic reprogramming, e.g., relative to a DC in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits induction of cell survival mechanisms, e.g., relative to a DC in a subject that has not been administered a composition described herein.

[0279] In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits induction of cell death mechanisms, e.g., relative to a DC

in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition 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 in a subject that has not been administered a composition described herein. In some embodiments, a modified DC in a subject that has been administered a composition described herein exhibits one, two, three, or four of improved duration of CAR, fusion protein, and/or peptide agent expression, improved stability of the CAR, fusion protein, and/or peptide agenton the cell surface, increased level of CAR, fusion protein, and/or peptide agent expression, or decreased background activity of the CAR, fusion protein, and/or peptide agent, e.g., relative to a DC in a subject that has not been administered a composition described herein.

EXEMPLARY SEQUENCES

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

Name	Uniprot	Amino Acid Sequence	Notes
IFN-α2	P01563	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLH EMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE **(SEQ ID NO: 1)**	Signal peptide removed
IFN-β	P01574	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDA ALTIYEMLQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTR GKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN **(SEQ ID NO: 2)**	Signal peptide removed
IFN-γ	P01579	QDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKL FKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHE LIQVMAELSPAAKTGKRKRSQMLFRG **(SEQ ID NO: 3)**	Signal peptide removed, propeptide removed
TNF-α	P01375	VRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGL YLIYSQVLFKGQGCPSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKP WYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL **(SEQ ID NO: 4)**	Soluble form (TMD removed) - Wang et al 1985
IL-1β	P01584	APVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDK IPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEF ESAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSS **(SEQ ID NO: 5)**	Propeptide removed for mature form
IL-6	P05231	VPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMCESSKEALAE NNLNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQ MSTKVLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKEF LQSSLRALRQM **(SEQ ID NO: 6)**	Signal peptide removed
IL-12 subunit p35	p29459	RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKT STVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVE FKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKI KLCILLHAFRIRAVTIDRVMSYLNAS **(SEQ ID NO: 7)**	Signal peptide removed

IL-12 subunit p40	P29460	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQ VKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAK NYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSV ECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNS RQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNAS ISVRAQDRYYSSSWSEWASVPCS **(SEQ ID NO: 8)**	Signal peptide removed
GM-CSF		MWLQSLLLLGTVACSISAPARSPSPSTQPWEHVNAIQEARRLLNLSRDTAAEMNETV EVISEMFDLQEPTCLQTRLELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSCA TQIITFESFKENLKDFLLVIPFDCWEPVQE **(SEQ ID NO: 174)**	

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

IL-4	P05112	HKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTEKETFCRAATVLRQFYSHH EKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERL KTIMREKYSKCSS **(SEQ ID NO: 9)**	Signal peptide removed
IL-10	P22301	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFK GYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPC ENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN **(SEQ ID NO: 10)**	Signal peptide removed
IL-13	P35225	LTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALE SLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF REGRFN **(SEQ ID NO: 11)**	Signal peptide removed
IL-18	Q14116	YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQPR GMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESS SYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED **(SEQ ID NO: 12)**	Signal peptide removed

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

IFNAR1	P17181	KNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNITS TKCNFSSLKLNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEAEDKAI VIHISPGTKDSVMWALDGLSFTYSLVIWKNSSGVEERIENIYSRHKIYKLSPETTYCLK	Signal peptide removed

		VKAALLTSWKIGVYSPVHCIKTTVENELPPPENIEVSVQNQNYVLKWDYTYANMTF QVQWLHAFLKRNPGNHLYKWKQIPDCENVKTTQCVFPQNVFQKGIYLLRVQASDG NNTSFWSEEIKFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQSGNTPVIQDYPLIYEIIF WENTSNAERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFSDAVCEKT KPGNTSKIWLIVGICIALFALPFVIYAAKVFLRCINYVFFPSLKPSSSIDEYFSEQPLKNL LLSTSEEQIEKCFIIENISTIATVEETNQTDEDHKKYSSQTSQDSGNYSNEDESESKTSE ELQQDFV **(SEQ ID NO: 13)**
IFNAR2	P48551	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNC ANTTRSFCDLTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPEFEIVG FTNHINVMVKFPSIVEEELQFDLSLVIEEQSEGIVKKHKPEIKGNMSGNFTYIIDKLIPN TNYCVSVYLEHSDEQAVIKSPLKCTLLPPGQESESAESAKIGGIITVFLIALVLTSTIVTL KWIGYICLRNSLPKVLNFHNFLAWPFPNLPPLEAMDMVEVIYINRKKKVWDYNYDD ESDSDTEAAPRTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEEPDLPEVDVELP TMPKDSPQQLELLSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFNVDLNSVFLRVLD DEDSDDLEAPLMLSSHLEEMVDPEDPDNVQSNHLLASGEGTQPTFPSPSSEGLWSED APSDQSDTSESDVDLGDGYIMR **(SEQ ID NO: 14)**
IFNGR1	P15260	EMGTADLGPSSVPTPTNVTIESYNMNPIVYWEYQIMPQVPVFTVEVKNYGVKNSEW IDACINISHHYCNISDHVGDPSNSLWVRVKARVGQKESAYAKSEEFAVCRDGKIGPPK LDIRKEEKQIMIDIFHPSVFVNGDEQEVDYDPETTCYIRVYNVYVRMNGSEIQYKILT QKEDDCDEIQCQLAIPVSSLNSQYCVSAEGVLHVWGVTTEKSKEVCITIFNSSIKGSL WIPVVAALLLFLVLSLVFICFYIKKINPLKEKSIILPKSLISVVRSATLETKPESKYVSLIT SYQPFSLEKEVVCEEPLSPATVPGMHTEDNPGKVEHTEELSSITEVVTTEENIPDVVPG SHLTPIERESSSPLSSNQSEPGSIALNSYHSRNCSESDHSRNGFDTDSSCLESHSSLSDS EFPPNNKGEIKTEGQELITVIKAPTSFGYDKPHVLVDLLVDDSGKESLIGYRPTEDSKE FS **(SEQ ID NO: 15)**
IFNGR2	P38484	APPDPLSQLPAPQHPKIRLYNAEQVLSWEPVALSNSTRPVVYQVQFKYTDSKWFTAD IMSIGVNCTQITATECDFTAASPSAGFPMDFNVTLRLRAELGALHSAWVTMPWFQHY RNVTVGPPENIEVTPGEGSLIIRFSSPFDIADTSTAFFCYYVHYWEKGGIQQVKGPFRS NSISLDNLKPSRVYCLQVQAQLLWNKSNIFRVGHLSNISCYETMADASTELQQVILIS VGTFSLLSVLAGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPTQPILEALDKDSS PKDDVWDSVSIISFPEKEQEDVLQTL **(SEQ ID NO: 16)**	Signal peptide removed

TNFR1	P19438	LVPHLGDREKRDSVCPQGKYIHPQNNSICCTKCHKGTYLYNDCPGPGQDTDCRECES GSFTASENHLRHCLSCSKCRKEMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQ CFNCSLCLNGTVHLSCQEKQNTVCTCHAGFFLRENECVSCSNCKKSLECTKLCLPQI ENVKGTEDSGTTVLLPLVIFFGLCLLSLLFIGLMYRYQRWKSKLYSIVCGKSTPEKEG ELEGTTTKPLAPNPSFSPTPGFTPTLGFSPVPSSTFTSSSTYTPGDCPNFAAPRREVAPP YQGADPILATALASDPIPNPLQKWEDSAHKPQSLDTDDPATLYAVVENVPPLRWKEFV RRLGLSDHEIDRLELQNGRCLREAQYSMLATWRRRTPRREATLELLGRVLRDMDLL GCLEDIEEALCGPAALPPAPSLLR **(SEQ ID NO: 17)**	Signal peptide removed. Membrane bound form
TNFR2	P20333	LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCE DSTYTQLWNWVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCR LCAPLRKCRPGFGVARPGTETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGN ASMDAVCTSTSPTRSMAPGAVHLPQPVSTRSQHTQPTPEPSTAPSTSFLLPMGPSPPAE GSTGDFALPVGLIVGVTALGLLIIGVVNCVIMTQVKKKPLCLQREAKVPHLPADKAR GTQGPEQQHLLITAPSSSSSSLESSASALDRRAPTRNQPQAPGVEASGAGEARASTGS SDSSPGGHGTQVNVTCIVNVCSSSDHSSQCSSQASSTMGDTDSSPSESPKDEQVPFSK EECAFRSQLETPETLLGSTEEKPLPLGVPDAGMKPS **(SEQ ID NO: 18)**	Signal peptide removed. Membrane bound form
IL-1R1	P14778	LEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIH QHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKL PVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIVMNVAE KHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVSPANETMEVDLGSQIQLI CNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNISEIESRF YKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCSVFIYKIFKIDIVLW YRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEKQCGYKLF IYGRDDYVGEDIVEVINENVKKSRRLIIILVRETSGFSWLGGSSEEQIAMYNALVQDGI KVVLLELEKIQDYEKMPESIKFIKQKHGAIRWSGDFTQGPQSAKTRFWKNVRYHMP VQRRSPSSKHQLLSPATKEKLQREAHVPLG **(SEQ ID NO: 19)**	Signal peptide removed. Membrane bound form
IL-1R3	Q9NPH3	SERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLIWYWTRQDR DLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRNTTYCSKVAFPLEVVQK DSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWYMGCYKIQNFNNVIP EGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVVGSPKNAVPPVIHSPND HVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTINESISHSRTED	Signal peptide removed

		ETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPRYTVELACGFGA TVLLVVILIVVYHVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAEEEEFVLL TLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSFIQKSRRLLVVLSPNYVLQGTQALL ELKAGLENMASRGNINVILVQYKAVKETKVKELKRAKTVLTVIKWKGEKSKYPQGR FWKQLQVAMPVKKSPRRSSSDEQGLSYSSLKNV **(SEQ ID NO: 20)**	
IL-6Ra	P08887	LAPRRCPAQEVARGVLTSLPGDSVTLTCPGVEPEDNATVHWVLRKPAAGSHPSRWAG MGRRLLLRSVQLHDSGNYSCYRAGRPAGTVHLLVDVPPEEPQLSCFRKSPLSNVVCE WGPRSTPSLTTKAVLLVRKFQNSPAEDFQEPCQYSQESQKFSCQLAVPEGDSSFYIVS MCVASSVGSKFSKTQTFQGCGILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSF YRLRFELRYRAERSKTFTTWMVKDLQHHCVIHDAWSGLRHVVQLRAQEEFGQGEW SEWSPEAMGTPWTESRSPPAENEVSTPMQALTTNKDDDNILFRDSANATSLPVQDSS SVPLPTFLVAGGSLAFGTLLCIAIVLRFKKTWKLRALKEGKTSMHPPYSLGQLVPERP RPTPVLVPLISPPVSPSSLGSDNTSSHNRPDARDPRSPYDISNTDYFFPR **(SEQ ID NO: 21)**	Signal peptide removed. Membrane bound form
gp130	P40189	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQY TIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKK MRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVW VEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILK YNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDW SEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLT RWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVM DLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLR GNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWD QLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDE GGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPD PSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLF KKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPS VQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDISHF ERSKQVSSVNEEDFVRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERF ETVGMEAATDEGMPKSYLPQTVRQGGYMPQ **(SEQ ID NO: 22)**	Signal peptide removed

IL-12-Rβ1	P42701	CRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECSWQYEGPTAGVSHFLRCCL SSGRCCYFAAGSATRLQFSDQAGVSVLYTVTLWVESWARNQTEKSPEVTLQLYNSV KYEPPLGDIKVSKLAGQLRMEWETPDNQVGAEVQFRHRTPSSPWKLGDCGPQDDD TESCLCPLEMNVAQEFQLRRRQLGSQGSSWSKWSSPVCVPPENPPQPQVRFSVEQLG QDGRRRLTLKEQPTQLELPEGCQGLAPGTEVTYRLQLHMLSCPCKAKATRTLHLGK MPYLSGAAYNVAVISSNQFGPGLNQTWHIPADTHTEPVALNISVGTNGTTMYWPARA QSMTYCIEWQPVGQDGGLATCSLTAPQDPDPAGMATYSWSRESGAMGQEKCYYITI FASAHPEKLTLWSTVLSTYHFGGNASAAGTPHHVSVKNHSLDSVSVDWAPSLLSTCP GVLKEYVVRCRDEDSKQVSEHPVQPTETQVTLSGLRAGVAYTVQVRADTAWLRGV WSQPQRFSIEVQVSDWLIFFASLGSFLSILLVGVLGYLGLNRAARHLCPPLPTPCASSA IEFPGGKETWQWINPVDFQEEASLQEALVVEMSWDKGERTEPLEKTELPEGAPELAL DTELSLEDGDRCKAKM **(SEQ ID NO: 23)**	Signal peptide removed
IL-12-Rβ2	Q99665	KIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFHYSRRNKLILYKFDRRINFHH GHSLNSQVTGLPLGTTLFVCKLACINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQGT VACTWERGRDTHLYTEYTLQLSGPKNLTWQKQCKDIYCDYLDFGINLTPESPESNFT AKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQKASVSRCTLYWRDEGLVLLNR LRYRPSNSRLWNMVNVTKAKGRHDLLDLKPFTEYEFQISSKLHLYKGSWSDWSESL RAQTPEEEPTGMLDVWYMKRHIDYSRQQISLFWKNLSVSEARGKILHYQVTLQELT GGKAMTQNITGHTSWTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGLLAPR QVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNWLRSRPYN VSALISENIKSYICYEIRVYALSGDQGGCSSILGNSKHKAPLSGPHINAITEEKGSILISW NSIPVQEQMGCLLHYRIYWKERDSNSQPQLCEIPYRVSQNSHPINSLQPRVTYVLWM TALTAAGESSHGNEREFCLQGKANWMAFVAPSICIAIIMVGIFSTHYFQQKVFVLLAA LRPQWCSREIPDPANSTCAKKYPIAEEKTQLPLDRLLIDWPTPEDPEPLVISEVLHQVT PVFRHPPCSNWPQREKGIQGHQASEKDMMHSASSPPPPRALQAESRQLVDLYKVLES RGSDPKPENPACPWTVLPAGDLPTHDGYLPSNIDDLPSHEAPLADSLEELEPQHISLSV FPSSSLHPLTFSCGDKLTLDQLKMRCDSLML **(SEQ ID NO: 24)**	Signal peptide removed

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

IL-4Rα	P24394	MKVLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENNGGA GCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPRAPGNLTVHTNVSD TLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLKSGIS YRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCY VSITKIKKEWWDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLL PCFLEHNMKRDEDPHKAAKEMPFQGSGKSAWCPVEISKTVLWPESISVVRCVELFEA PVECEEEEEVEEEKGSFCASPESSRDDFQEGREGIVARLTESLFLDLLGEENGGFCQQ DMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPWGKEQPLHLEPSPPASPTQSPDNLT CTETPLVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTTV PQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGLGPP GEAGYKAFSSLLASSAVSPEKCGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGL DREPPRSPQSSHLPSSSPEHLGLEPGEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSAL TCHLCGHLKQCHGQEDGGQTPVMASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLE ASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTYMRVS **(SEQ ID NO: 25)**	Signal peptide removed. Membrane bound form
IL-2Rγc	P31785	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSSSEP QPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPRE PRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFLNHCLEHLVQYRTDW DHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSN TSKENPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFS AWSGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSPYWAPPCYTL KPET **(SEQ ID NO: 26)**	Signal peptide removed
IL-13Rα1	P78552	GGGGAAPTETQPPVTNLSVSVENLCTVIWTWNPPEGASSNCSLWYFSHFGDKQDKK IAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEGDPESAVTELQCIWHN LSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFGCSFDLTKVKDS SFEQHSVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNF ISRCLFYEVEVNNSQTETHNVFYVQEAKCENPEFERNVVENTSCFMVPGVLPDTLNTV RIRVKTNKLCYEDDKLWSNWSQEMSIGKKRNSTLYITMLLIVPVIVAGAIIVLLLYLK RLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWKKYDIYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 27)**	Signal peptide removed

IL-10R1	Q13651	HGTELPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSISNCSQTLS YDLTAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHN GFILGKIQLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTHKKVKHENFSLLTS GEVGEFCVQVKPSVASRSNKGMWSKEECISLTRQYFTVTNVIIFFAFVLLLSGALAYC LALQLYVRRRKKLPSVLLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLKVSPELKNLDL HGSTDSGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPPVLGDSCSSGSSNSTDSGI CLQEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSALGHHSPPE PEVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEESPLTDGLGPKFGRCLVDEAG LHPPALAKGYLKQDPLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSFAH DLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 28)**	Signal peptide removed
IL-10R2	Q08334	MVPPPENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMNTTLTECDF SSLSKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLA PKIENEYETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDFEVLRNLEPWTTYC VQVRGFLPDRNKAGEWSEPVCEQTTHDETVPSWMVAVILMASVFMVCLALLGCFAL LWCVYKKTKYAFSPRNSLPQHLKEFLGHPHHNTLLFFSFPLSDENDVFDKLSVIAEDS ESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 29)**	Signal peptide removed
IL-18Rα	Q13478	AESCTSRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYKSSGSQEHVELNPRSSSRIA LHDCVLEFWPVELNDTGSYFFQMKNYTQKWKLNVIRRNKHSCFTERQVTSKIVEVK KFFQITCENSYYQTLVNSTSLYKNCKKLLLENNKNPTIKKNAEFEDQGYYSCVHFLH HNGKLFNITKTFNITIVEDRSNIVPVLLGPKLNHVAVELGKNVRLNCSALLNEEDVIY WMFGEENGSDPNIHEEKEMRIMTPEGKWHASKVLRIENIGESNLNVLYNCTVASTGG TDTKSFILVRKADMADIPGHVFTRGMIIAVLILVAVVCLVTVCVIYRVDLVLFYRHLTR RDETLTDGKTYDAFVSYLKECRPENGEEHTFAVEILPRVLEKHFGYKLCIFERDVVPG GAVVDEIHSLIEKSRRLIIVLSKSYMSNEVRYELESGLHEALVERKIKIILIEFTPVTDFT FLPQSLKLLKSHRVLKWKADKSLSYNSRFWKNLLYLMPAKTVKPGRDEPEVLPVLS ES **(SEQ ID NO: 30)**	Signal peptide removed
IL-18Rβ	O95256	FNISGCSTKKLLWTYSTRSEEEFVLFCDLPEPQKSHFCHRNRLSPKQVPEHILPFMGSN DLSDVQWYQQPSNGDPLEDIRKSYPHIIQDKCTLHFLTPGVNNSGSYICRPKMIKSPY DVACCVKMILEVKPQTNASCEYSASHKQDLLLGSTGSISCPSLSCQSDAQSPAVTWY KNGKLLSVERSNRIVVDEVYDYHQGTYVCDYTQSDTVSSWTVRAVVQVRTIVGDT KLKPDILDPVEDTLEVELGKPLTISCKARFGFERVFNPVIKWYIKDSDLEWEVSVPEA	Signal peptide removed

		KSIKSTLKDEIIERNIILEKVTQRDLRRKFVCFVQNSIGNTTQSVQLKEKRGVVLLYILL GTIGTLVAVLAASALLYRHWIEIVLLYRTYQSKDQTLGDKKDFDAFVSYAKWSSFPSE ATSSLSEEHLALSLFPDVLENKYGYSLCLLERDVAPGGVYAEDIVSIIKRSRRGIFILSP NYVNGPSIFELQAAVNLALDDQTLKLILIKFCYFQEPESLPHLVKKALRVLPTVTWRG LKSVPPNSRFWAKMRYHMPVKNSQGFTWNQLRITSRIFQWKGLSRTETTGRSSQPKE W **(SEQ ID NO: 31)**	

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

Name	Uniprot	Codon Optimized Sequence	Notes
IFN-α2	P01563	Tgcgaccttccacagacccattccctcggctctcgaagaactctgatgttgctggcccagatgcggaagatttctcttttctcatgtctg aaagacaggcacgactttggttttccccaggaggagttcggaaaccagttccagaaagcggaaaccattcctgtgctgcacgaaat gatccaacaaattttcaacctgttttcaactaaagatagctccgctgcatgggacgagacactcctcgataagttttatacagagctttac cagcagttaaatgatctggaagcttgtgtcatccaaggggtcggcgtaaccgagacgcccctgatgaaggaggatagcatactggc agtgcggaagtacttccagaggatcaccctctatctaaaggaaaaaaagtacagtccgtgcgcctgggaagtggttagagccgaaa tcatgcgtagcttttccttatctacaaatttgcaggagtcgttgcgcagtaaagag **(SEQ ID NO: 32)**	Signal peptide removed
IFN-β	P01574	Atgagttataatttactcggatttctacagcggtctagcaacttccaatgtcagaagctgctgtggcaactcaacggcaggctggagta ctgcctcaaagatagaatgaactttgatattcccgaagaaatcaagcagcttcagcagttccagaaagaggacgccgcactaaccat atacgagatgctgcagaacattttcgctatattcagacaggactcgtcctctactggatggaatgagaccatcgtcgagaatttgctgg ccaatgtgtatcatcaaattaaccacctcaagacggtgcttgaagaaaagttggaaaaagaggacttcactagaggcaaactgatgtc atcccttcacctcaaacgctactatgggaggatcctgcactacttaaaggcgaaggagtatagccattgcgcttggacaatcgttcgc gtagagattctgcggaatttttactttatcaatcgtttgacaggttacctgcgaaac **(SEQ ID NO: 33)**	Signal peptide removed
IFN-γ	P01579	Caggatccctacgtgaaggaagcagaaaatctcaaaaagtatttcaatgcgggccatagcgatgtggccgataacggcaccctgtt tctggggattcttaagaattggaaagaggagtctgataggaagattatgcagtcccagatcgtgagcttctatttcaagctgttcaaaaa cttcaaagacgaccagtcgatccaaaaatctgttgagacaataaaagaggacatgaatgtgaagttttttaattcaaacaaaaagaagc gcgacgattttgagaaattaacgaactactccgtcaccgacttgaacgtacaacgaaaggctattcacgaactaatccaggtcatggc tgaactgagtcctgccgccaagactggtaagcgtaaacggagtcagatgctctttagagga **(SEQ ID NO: 34)**	Signal peptide removed, propeptide removed
TNF-α	P01375	Gtgcgatcttcaagccggacaccctcagacaagccagtggcacacgtggtagcgaacccacaagctgaggggcagctccagtg gctcaatcggcgtgccaacgccctgttagccaatggggtcgagcttagggacaaccaacttgtggtaccctcggaaggattatactt gatttacagtcaggtgctgttcaaaggacagggctgcccttccacacatgttctgctcactcacacgatctcccgcattgcagtgtctta	Soluble form (TMD removed) - Wang et al 1985

		tcagaccaaggtcaacttgctaagcgctatcaaaagtccatgtcagagagagaccccggaggggtgctgaggctaagccttggtacg aacctatttatctgggcggagtctttcaactggaaaaaggtgatagactgagcgcagagatcaataggcccgattacctggacttcgc cgaatccggccaggtttatttgggataatcgccctc **(SEQ ID NO: 35)**	
IL-1β	P01584	Gcgcctgtcagaagcctcaactgcacgctgaggactcacagcaaaaagagcctggtcatgagtggcccctacgagctgaaagca ctccaccttcagggcaggcatggaacaacaggtggtttctccatgtctttcgtacagggagaggagtctaacgataagatcccc gtggctttgggcttaaaagagaaaaacctgtatctgagctgtgtgctaaaggacgataagcccacacttcagctcgagtccgttgatc caaaaaattatccaaagaaagaaaatggaaaagcggtttgtgtttaacaagattgagattaataacaaattggaattcgaatcagcccag ttccctaattggtacatcagtacctctcaagccgaaaatatgccggtgtttctgggagggaccaagggtggccaggatataacagact tcactatgcagtttgtctcgtcc **(SEQ ID NO: 36)**	Propeptide removed for mature form
IL-6	P05231	Gtgccgcccgggggaagatagcaaggatgtggctgctcctcacaggcagccactgacaagcagcgagagaatcgacaagcaaat aaggtatattcttgatggaatcagcgcgctgcgaaaggagacatgtaacaagtcgaatatgtgcgagtcttccaaagaagcacttgct gaaaataatctgaacctcccaaaaatggccgagaaagacggctgctttcagtccggtttaacgaggagacttgtttagtaaagattat aacgggcttgttggaattcgaagtctacctagaatacctccaaaatagattcgagagtagtgaggaacaggcccgcgctgttcagat gtcaacaaaagtgttgatccaattcctgcagaaaaaagccaagaacttagatgcaatcaccacacctgacccactactaccaatgcctct ctgctcaccaagctgcaagcccagaaccagtggctgcaggacatgactacccatctaattctgcggtctttaaggagttcctccagtc atccctgcgtgcacttcggcagatg **(SEQ ID NO: 37)**	Signal peptide removed
IL-12 subunit p35	p29459	Cgaaatctgccagtggctacccccgacccgggcatgtttccctgcctccatcatagccagaatctgctcagagcggtcagcaacat gctacagaaggcccgccagaccttagagtttaccctgcacctctgaggaaatcgatcacgaagacatcaccaaagataagactag caccgttgaagcctgtctcccattggaacttacaaaaaaatgaatcttgtctgaattccagagagacatctttatcactaatggaagttgc ctcgccagtcggaaaacttccttcatgatggcccctgtgtctgagttcaatctacgaggatcttaagatgtatcaagtggaattcaaaacg atgaacgcaaaactgttgatggatcctaagaggcagatattttggatcagaacatgttagctgtgatcgacgagctgatgcaagcact caacttcaactcagagacagtcccccagaagtcctccctggaggagcctgacttctacaagacgaaaattaagctatgcattctgcttc acgcattcaggatacgggccgtaacaattgaccgtgtgatgagctatctgaacgcttcg **(SEQ ID NO: 38)**	Signal peptide removed
IL-12 subunit p40	P29460	Atctgggagctcaaaaaggatgtttatgtggtcgaacttgactggtaccccggacgcaccaggggagatggtggttgttgacctgcga caccccgaagaggaggacgggattacatggacttttggaccagtccagtgaagtcctgggctcgggaaagaccctgactatccaggtg aaggagttcggagatgctggacaatatacatgccacaagggcgggggaagtttgagccattccctcctgctgctgcataaaaaagag gatggtatttggagcactgatattctgaaagaccagaaggaacccaagaacaaaaacttttctgcggtgtgaggccaagaattacagtg gaagattcacctgttggtggttaaccacaatctctaccgatcttacctttccgtcaaatcaagtcgcggcagcgatccacagggc gtgacgtgcggcgctgccacactaagcgcggagagagtgcggggtgacaacaaggaatacgagtactccgttgagtgtcaagaa gactctgcatgccctgccgcagaggaatcattaccgatcgaagtaatggtggatgctgttcacaaactgaagtatgaaaactacactt cttcatttttcataagggacattatcaagcctgatcctccaaagaacctccaacttaaaccactcaagaatagccgtcaggtagaggtgt	Signal peptide removed

		cctgggagtaccccgatacctggtcaacgccccactcatatttctccctgacgttctgtgtgcaggtgcaggggaaatccaagaggg agaagaaagacagggtctttacagataagacatctgccactgtcatctgcagaaaaaatgcctctatatccgtgcgagcccaggacc gctactattctagtagctggagcgagtgggctagtgtaccttgttcg **(SEQ ID NO: 39)**	
GM-CSF		ATGTGGCTGCAGAGCCTGCTGCTCTTGGGCACTGTGGCCTGCAGCATCTCTGCAC CCGCCCGCTCGCCCAGCCCCAGCACGCAGCCCTGGGAGCATGTGAATGCCATCC AGGAGGCCCGGCGTCTCCTGAACCTGAGTAGAGACACTGCTGCTGAGATGAATG AAACAGTAGAAGTCATCTCAGAAATGTTTGACCTCCAGGAGCCGACCTGCCTAC AGACCCGCCTGGAGCTGTACAAGCAGGGCCTGCGGGGCAGCCTCACCAAGCTC AAGGGCCCCTTGACCATGATGGCCAGCCACTACAAGCAGCACTGCCCTCCAACC CCGGAAACTTCCTGTGCAACCCAGATTATCACCTTTGAAAGTTTCAAAGAGAAC CTGAAGGACTTTCTGCTTGTCATCCCCTTTGACTGCTGGGAGCCAGTCCAGGAGT GA **(SEQ ID NO: 175)**	

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

IL-4	P05112	Cacaagtgtgatattacactccaagaaataatcaagaccctgaacagcctaaccgagcagaaaactctctgtacggaattgaccgtta ccgatatcttcgcagctagtaagaatacaactgaaaaagagacgttttgtcgtgccgccacagtcctgaggcagttttattcacatcacg agaaagacacccggtgccttggggcaactgcccaacagtttcatcgccacaaacagctgatcagattcttgaagcggctggacagga atctctggggattagctggcctgaattcttgccccgtgaaggaggcgaaccagagcactctggagaacttcctggaacgacttaagac aattatgagagagaagtactccaaatgctcctct **(SEQ ID NO: 40)**	Signal peptide removed
IL-10	P22301	Tcacccggacagggtactcaatctgaaaatagttgcacccattttccaggaaatctgcctaacatgctgagggacttacgcgatgcattt tcgcgtgtaaaaacattctttcagatgaaagatcaactggataacctgttgctaaaagagagcctgcttgaggatttcaagggctatctg ggctgtcaggcgctctccgaaatgattcaattctacctcgaagaggtgatgccccaggccgagaaccaggacccagacatcaaggc ccacgtgaattctctgggggagaatctgaaaacgctcagattgcgactcagacggtgccacaggtttttaccttgtgaaaacaagagc aaagccgttgagcaggtcaagaacgcttttaataagcttcaggaaaaagggatctataaggcaatgtccgagttcgacatattcattaat tacattgaggcttacatgaccatgaagatccggaac **(SEQ ID NO: 41)**	Signal peptide removed
IL-13	P35225	Ttaacatgtctgggcgggttcgcctcacctggaccagttccccttcaaccgctctcagagaactgattgaggagctcgtcaatatcac ccagaaccaaaaagccccactctgcaatggaagtatggtgtggtctattaacttgactgccggcatgtactgtgccgcactggagtcttt gatcaacgtgtccgggtgcagtgcaatcgaaaagacgcagcggatgctgagcggcttttgcccccacaaggtgagcgctggtcagtt ttccagccttcacgtgcgagatacaaagatagaagtagcgcagttcgtcaaggacctgctgctgcatcttaaaaaactatttcgcgagg gtaggttcaat **(SEQ ID NO: 42)**	Signal peptide removed

IL-18	Q14116	Tattttggcaaactcgaaagtaagctgagcgtgattcggaatcttaacgatcaggtgttattcatcgatcaaggcaacagaccactctttgaagatatgacagattcagactgtagggataatgcccctaggaccatctttattataagcatgtataaggactctcagccccgcggtatggcagtaacgattagcgttaagtgcgagaagatttctacactttcatgcgaaaacaaaatcatctccttcaaagagatgaaccctcccgataatatcaaagataccaagtcggacataattttctttcagagatccgtcccaggacacgacaataagatgcaattcgaatccagcagttacgagggatactttctggcttgtgagaaggaacgtgacttgttcaaactgatcctgaagaaagaggacgagctaggggaccgatctatcatgttcactgtgcagaacgaggac **(SEQ ID NO: 43)**	Signal peptide removed

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

IFNAR1	P17181	aagaacctgaaatccccacagaaagtcgaggtggacatcatcgatgacaatttcatcttaagatggaaccgtagcgatgagtccgtcggaaatgtcacattttcttttgattatcagaagaccgggatggacaactggattaagctgtccggttgccagaacataaccagtaccaagtgtaacttcagcagcctcaaactcaatgtatatgaggaaatcaagctgaggatccgggccgagaaggaaaacacaagctcctggtatgaagttgattcatttactccatttcgaaaagcgcaaataggacccccggaagttcacctcgaggctgaagataaagcaattgtaatacacatatcgcctggcaccaaggactctgtgatgtgggctttagatgggctgtcattcacgtacagcctggtgatctggaagaacagttctggggtggaggagagaatagaaaacatttatagtcgccacaaaatctacaaattgtcacccgaaacaacctattgcctgaaggtcaaggcggcactattgacgtcctggaagatcggcgtgtactcaccagtgcattgtataaagacaacagtggaaaacgagcttcccccgccggagaatattgaggtttccgtgcagaatcagaattatgtgttgaagtgggactacacatatgccaatatgaccttccaggttcaatggcttcatgcatttctgaaaagaaaccctggtaaccacctttacaaatggaagcagattcctgactgcgagaatgtcaagaccacacagtgcgtgtttcctcaaaacgttttccagaaaggcatctatctgctacgggtccaggcttccgatggcaataatacctcattttggagcgaggaaattaaattcgacactgaaatccaagccttcctactccctcccgtatttaacatcaggagtctgtctgatagcttccatatttacatcggtgctcccaagcagtctggaaacactcccgtgatccaggattacccccctcatctacgagatcattttctgggaaaacacctctaacgccgaacggaagattatagagaagaaaactgacgtcactgtgcctaacctgaaaccattaactgtctattgcgtcaaagctagggcccacaccatggatgaaaaactgaacaagtctagcgtgttcagcgacgcagtttgtgagaaaacgaagccaggaaatacttctaagatttggcttatcgtgggcatttgtatcgctctgttcgcactgccctttgtaatctacgccgccaaggtttttctccgctgtattaattatgtgtttttcccatccctgaagccatcatcgtcgattgacgagtacttctctgagcaacctcttaaaaacctgttgttgtccaccagtgaagagcagattgagaaatgcttcattatcgaaaatatttcaacaatcgccacagtggaggagacgaatcagaccgacgaggaccataagaagtacagcagtcagacatctcaggattccgggaattacagcaatgaagatgaaagtgaatccaaaactagcgaggagctccaacaggactttgtg **(SEQ ID NO: 44)**	Signal peptide removed
IFNAR2	P48551	atcagctacgactcccccgattacaccgacgagtcctgtaccttaaaatctccctacgtaacttcaggtccattctctcctgggaactgaaaaaccatagcattgtgccgactcactatacactgctgtataccataatgtctaaacccgaggatctgaaggtggtgaagaactgtgcgaacaccacaagatccttctgcgacctgacagatgagtggcgatctacccatgaagcctacgtcacggtcctcgagggcttcagcggtaataccacacttttcagctgctcacataacttttggttggccatcgatatgtcctttgaaccacccgagttcgagattgtcggtttcacaaac	Signal peptide removed

	cacatcaatgtcatggtgaaatttccttctattgtcgaggaagaactccagtttgatttgagcctcgtgattgaggagcagtcagaggggaa	
	tcgtgaagaagcataagcccgaaataaagggaaatatgagtgggaacttcacttacataatcgacaagctcatcccccaacacgaatta	
	ttgtgtgtcagtgtatctcgagcactcggatgagcaagccgtgatcaagtctcccacttaagtgcactctcctgccgccaggccaggagt	
	cagagagcgctgaatcggctaagatagggcgggatcattaccgtctctcctcatcgcactggtgttgactcttctactattgttaccctgaagtg	
	gatcggatacatctgcttgcgcaactctctgccaaaagttctaaacttcacaatttctggcctggccctcccaatcttcctcctctggga	
	ggccatggacatggttgaggttatctatataaatcggaaaaaaaaaagtctgggactacaattacgatgacgaaagtgactcagacacg	
	gaggccgcaccaaggacctctggaggggctatactatgcacggcctttaccgtgagaccttaggacaggcatctgctcacaagcact	
	gaaagccagctgattgacccagagagcgaggaagagcctgatctaccagaagtggatgtagagctgccgacaatgcctaaggact	
	ccccccaacagctcgaactgttgagcggcccttgtgaaaggcgcaaaagtcccttgcaagatccgttcctgaagaagactatagca	
	gtaccgaaggatccggcgtcggtcggattacattcaacgtggatttaaatagtgtatttttacgggttctggacgatgaggacagtgatgatct	
	ggaggcgcccttatgctgtcctcccatctggaggagatggtagacccgaagatccagataacgtgcagtctaatcaccttctggctt	
	ccgggaaggtactcagccaacctttcctagtcctttcttcagagggcttatggtcagaagacgcaccaagcgatcagtcagacacaa	
	gtgagagcgacgtagacctcgggggacgggtacattatgaga **(SEQ ID NO: 45)**	
IFNGR1	gaaatgggactgccgacttgggacctagcagtgtcccactcccaccaacgtgaccatcgagtcttataatatgaatcctattgtttatt	Signal peptide removed
	gggaatatcagatcatgcctcaggttccagtgttcactgttgaagtgaaaaattacggagtgaagaactcagagtggatagacgcttgc	
	ataaacatatctcaccattactgcaatatttccgaccaccacgtgggcgacccccagcaacagtttgtgggtcagagtgaaagctcgcgtgg	
	gccagaaggagagtgcttatgccaaaagcgaagaattcgccgtttgtagagatggcaagatcgggccccccaaattagacattcgca	
	aagaagaaaaacaaattatgatcgatatcttccatcccctctgtcttcgtcaacggcgacgaacaggaggtagattatgatccagagaca	
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IL-12-Rβ1	P42701	Signal peptide removed tgcagaactagcgaatgttgtttccaggaccccccgtatccgacgccgattccggaagcgcatccggaccacgtgacctgcggtgc tatcggatttctagcgatagtacgaatgctcatggcagtacgagggcccactgctgggtgagtcacttcttaagatgctgtttaagtt ccgggaggtgctgctatttcgccgcagggtcagctactcgactacagtttctgaccaggctggagtaagcgtgctttatacagtgaca ctgtgggtcgaatcctgggccaggaaccaaacggagaagtcacccgaggtgaccctgcaactgtataactcagtcaaatacgagcct cctctgggtgacattaaagtgtcgaaactcgccggacacagcttagaatggagtgggagaccccgataaccaggttggcgcagaggt gcagttccggcaccgaacacctcatctccttggaaactgggcgattgtggtccgcaggacgacgatacccgagagttgcttgtgtccc ctagagatgaatgtcgcacaggagtttcagctgaggaggcgtcagctcggcagccaaggcagttcttggtcaaaatggtcctccccc gtctgcgttcccccctgaaaatcctccacagccgcaggttcgattcagcgtggaacaactcgggcaggacgggagacgccgcttgact cttaaggagcaaccaacgcagctcgaactcccagaaggttgccaggcctggcacctggcaccgaggtgacctaccgtttgcagtt acatatgcttagttgccttgtaaggccaaggctacacggaccctcacctaggcaaaatgccatacctaagcggtgctgcatacaacg tggcggtcatttcttccaaccagttcggaccccggtctgaatcagacctggcacatcccccgcagatacccatacccgaacctgtggcgct gaatatcagcgtgggcacaaatggcactacgatgtattggccggcccgcgctcaatctatgacttactgcatcgaatggcagcctgttg ggcaagatggaggactcgcgacatgcagccttactgccccgcaggaccctgatccagcaggtatggccacttattcttggagccgcg agtccgggccatgggacaggagaagtgttactacatcaccatatttgcgtcagctcatccagaaaagctgaccctgtggtcaaccgt tctgagcatataccacttcgggggcaatgcgtccgctgcaggcacccccacaccacgtgtcggtgaaaaaccactctctggacagtgt gagtgttgactgggccccaagcctgttgtccacatgtcccgggggtgctcaaggaatatgttgtccgctgtcgagacgaggactccaaa caagtgtcggaacatcccgtacagccaacggagacccaagtcactctgtctggactgagagccggcgtggcctacacagtccaagt gcgggcagatacagcttggttacgggggcgtatggagccagccacaaaggttcagcattgaggtacaggtctctgattggttgatttttt tgccagtctgggcagtttctctctatcctgttggtcgagtgttgggctatctgggactgaatcgcgccgccagacatctgtgccccc actcccaacccccatgtgcctcctccgccatagaatttcctgggggtaaagagacatggcagtggatcaaccctgtagacttccaggag gaggctagcctccaggaagccctgttgtggaaatgtcatgggataaaggcgagagaagaacggaacctctcgagaagactgaacttcc cgagggagctcctgagctcgcacttgacacagaactgtctttagaggatgggataggtgtaaggctaagatg **(SEQ ID NO: 54)**
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	aagtgaccgcggtgaacagcctgggcagcagcagcctgccgagcacctttaccttctggatattgtgcgcccgctgccgccgt gggatattcgcattaaatttcagaaagcgagcgtgagccgctgcacccgtgtattggcgcgatgaaggcctggtgctgctgaaccgcct gcgctatcgcccgagcaacagccgcctgtggaacatggtgaaccaaagcgaaaggccgccatgatctgctggatctgaaac cgtttaccgaatatgaatttcagattagcagcaaactgcatctgtataaaggcagctggagcgattggagcgaaagcctgcgcgcgca gaccccggaagaagaaccgaccggcatgctggatgtgtggtatatgaaacgccatattgattatagccgccagcagattagcctgtttt ggaaaaacctgagcgtgagcgaagcgcgcggcaaaattctgcattatcaggtgaccctgcaggaactgaccggcgcaaagcgat gacccagaacattaccggccataccagctggaccaccgtgattccgcgcaccggcaactgggcggtggcggtgagcgcggcgaa cagcaaaggcagcagcctgccgacccgcattaacattatgaacctgtgcgaagcgggcctgctggcgccgccgccaggtgagcgc gaacagcgaaggcatggataacattctggtgaccctggcagccgccgcgcaaagatccgagcgcggtgcaggaatatgtggtggaa tggcgcgaactgcatccgggcggcgatacccaggtgccgctgaactggctgctgcgcagccgcccgtataacgtgagcgcgctgatta gcgaaaacattaaagctatatttgctatgaaattcgcgtgtatgcgctgagcggcgatcagggcggctgcagcagcattctgggcaa cagcaaacataaagcgccgctgagcggcccgcatattaacgcgattaccgaaagaaaaaggcagcattctgattagctggaacagca ttccggtgcaggaacagatgggctgcctgctgcattatctgcatttattggaaagaacgcgatagcaacagccgcagctgtgcg aaattccgtatcgcgtgagccagaacagccatccgattaacagcctgcagccgcgcgtgacctatgtgctgtggatgaccgcgctga ccgcggcgggcgaaagcagccatggcaacgaacgcgaattttgcctgcagggcaaagcgaactggatggcgtttgtggcgccga gcatttgcattgcgattattatgtgggcatttttagcaccattatttcagcagaaagtgtttgtgctgctggcgggcgctgcgcccgcag tggtgcagccgcgaaattccggatccggcgaacagcacctgcgcgaaaaaatatccgattgcggaagaaaaacccagctgccgc tggatcgcctgctgattgattggccgacccgggaagatccggaaccgctggtgattagcgaagtgctgcatcaggtgaccccggtgtt tcgccatccgccgtgcagcaactggccgcagcgcgaaaaaggcattcagggccatcaggcgagcgaaaaagatatgatgcatagc gcgagcagcccgccgccgccgccgctgcaggcggaaagccgcccagctggtggatctgtataaagtgctggaaagccgcgg cagcgatccgaaaccggaaaaccgggcgtgcccgtggaccgtgctgccggcgggcgatctgccgacccatgatggctatctgccg agcaacattgatgatctgccgagccatgaagcgccgctggcggataggcctggaagaactggaaccgcagcatattagcctgagcgt gtttccgagcagcagcctgcatccgctgacctttagctgccggcgataaaactgaccctggatcagctgaaaatgcgctgcgatagcctg atgctg **(SEQ ID NO: 55)**	

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

IL-4Rα	P24394	atgaaagtgctgcaggaaccgacctgcgtgagcgattatatgagcattagcacctgcgaatggaaaatgaacggcccgaccaactg cagcaccgaactgcgcctgctgtatcagctggtgttctgctgagcgaagcgcataccttgcattccggaaaacaacggcggcgcgg gctgcgtgtgccatctgctgatggatgatgtggtgagcgcggataactatacccttggatctgtgggcgggccagcagctgctgtggaa aggcagctttaaaccgagcgaacatgtgaaaccgcgcgccgggcaacctgaccgtgcatcaccgtgagcgatacccctgctg	Signal peptide removed. Membrane bound form

		ctgacctggagcaacccgtatccgccggataactatctgtataaccatctgacctatgcggtgaacatttggagcgaaaacgatccgg cggattttcgcatttataacgtgacctatctggaaccgagcctgcgcattgcggcgagcaccctgaaaagcggcattagctatcgcgc gcgcgtgcgcgcgtgggcgcagtgctataacaccacctggagcgaatggagcccgagcaccaaatggcataacagctatcgcgaa ccgtttgaacagcatctgctgctgggcgtgagcgtgagctgcattgtgattctggcggtgtgcctgctgtgctatgtgagcattaccaaa attaaaaaagaatggtgggatcagattccgaacccggcgcgcagccgcctggtggcgattattattcaggatgcgcagggcagcca gtgggaaaaacgcagccgcggccaggaaccggcgaaatgcccgcattggaaaaactgcctgaccaaactgctgccgtgctttctg gaacataacatgaaacgcgatgaagatccgcataaagcggcgaaagaaatgccgtttcagggcagcggcaaaagcgcgtggtgcc cggtggaaattagcaaaaccgtgctgtggccggaaagcattagcgtggtgcgctgcgtggaactgtttgaagcgccggtggaatgc gaagaagaagaagaagtggaagaagaaaaaggcagcttttgcgcgagcccggaaagcagccgcgatgattttcaggaaggccgc gaaggcattgtggcgcgcctgaccgaaagcctgtttctggatctgctgggcgaagaaaacggcggcttttgccagcaggatatgggc gaaagctgcctgctgccgccgagcggcagcaccagcgcgcatatgccgtgggatgaatttccgagcgcgggcccgaaagaagcg ccgccgtggggcaaagaacagccgctgcatctggaaccgagcccgccggcgagcccgacccagagcccggataacctgacctg caccgaaaccccgctggtgattgcgggcaacccggcgtatcgcagctttagcaacagcctgagccagagcccgtgcccgcgcgaa ctgggcccggatccgctgctggcgcgccatctggaagaagtggaaccggaaatgccgtgcgtgccgcagctgagcgaaccgacc accgtgccgcagccggaaccggaaacctgggaacagattctgcgccgcaacgtgctgcagcatggcgcggcggcggcgccggt gagcgcgccgaccagcggctatcaggaatttgtgcatgcggtggaacagggcggcacccaggcgagcgcggtggtgggcctgg gcccgccgggcgaagcgggctataaagcgtttagcagcctgctggcgagcagcgcggtgagcccggaaaaatgcggctttggcg cgagcagcggcgaagaaggctataaaccgtttcaggatctgattccgggctgcccgggcgatccggcgccggtgccggtgccgct gtttacctttggcctggatcgcgaaccgccgcgcagcccgcagagcagccatctgccgagcagcagcccggaacatctgggcctg gaaccgggcgaaaaagtggaagatatgccgaaaccgccgctgccgcaggaacaggcgaccgatccgctggtggatagcctggg cagcggcattgtgtatagcgcgctgacctgccatctgtgcggccatctgaaacagtgccatggccaggaagatggcggccagaccc cggtgatggcgagcccgtgctgcggctgctgctgcggcgatcgcagcagcccgccgaccaccccgctgcgcgcgccggatccga gcccgggcggcgtgccgctggaagcgagcctgtgcccggcgagcctggcgccgagcggcattagcgaaaaaagcaaaagcag cagcagctttcatccggcgccgggcaacgcgcagagcagcagccagaccccgaaaattgtgaactttgtgagcgtgggcccgacc tatatgcgcgtgagc **(SEQ ID NO: 56)**	
IL-2Rγc	P31785	Ctgaacacaacaattctcacccctaacggcaacgaagacactaccgcagattttttcctcactactatgcccactgattccctttccgtgt cgaccttgccgctgccagaagtgcagtgcttcgtctttaatgttgagtatatgaattgtacatggaattctagcagcgaaccgcagccaa ccaatttgacattgcactactggtataaaaactcagataacgacaaagtgcagaagtgttcccactacttatttagcgaggaaataacctc tgggtgccagctgcagaagaaggagatccatctgtaccagaccttcgtcgtgcagctccaggatccacgggaaccacgccggcaa gctacccaaatgctaaagctgcaaaatctcgttatcccatgggcacctgagaatttgacacttcataagctgtcggaatcccagctgga gctcaattggaacaaccgtttcctcaaccattgtctggagcacctggtgcagtacagaaccgactgggaccatagttggacggagcag agtgtcgattatagacacaaattctcactaccctcagtggacgggcagaagaggtacacatttagagtaaggagtcggttcaatcccct	Signal peptide removed

		gtgcgggtccgccccaacactggagtgagtggtctcatcctattcactgggggcagcaacacgtccaaggagaaccctttcttgtttgctc tggaagctgttgtgatttcagtaggctctatggattaatcatcagcctcctgtgtgtctatttttggctggagcgaacaatgcccaggatc cccactctcaaaaatctggaagacttgtgacggagtatcacggcaacttcagcgcgtggtctggcgtctctaaaggtcttgccgaga gcctgcagcctgattacagtgagcgcttatgcctggtgagcgagataccacctaaaggaggagccctttggtgaaggaccgggggca tccccctgtaatcaacactcaccatactgggccccccctgctataccctaaagcctgaaact **(SEQ ID NO: 57)**
IL-13Rα1	P78552	Signal peptide removed ggcggcggcggcgcggccgaccgaaacccagccgccggtgaccaacctgagcgtgagcgtggaaaacctgtgcaccgtgat ttggacctggaacccgccggaaggcgcgagcagcaactgcagcctgtggtatttttagccatttggcgataaacagggataaaaaaatt gcgccggaaacccgccgcagcattgaagtgccgctgaacgaacgcatttgcctgcaggtgggcagccagtgcagccaccaacgaa agcgaaaaaccgagcattctggtggaaaaatgcattagcccgccggaaggcgatccggaaagcgcggtgaccgaactgcagtgca tttggcataacctgagctatatgaaatgcagctggctgccgggccgcaacaccagcccggataccaactaccctgtattattggcat cgcagcctggaaaaaattcatcagtgccgaaaacatttttcgcgaaggccagtatttttggctgcagctttgatctgaccaaagtgaaagat agcagctttgaacagcatagcgtgcagattatggtgaaagataacgcgggcaaaattaaaccgagctttaacattgtgccgctgacca gccgcgtgaaaccggatccgccgcatattaaaaacctgagctttcataacgatgatctgtatgtgcagtgggaaaacccgcagaaacttt attagccgctgcctgtttttatgaagtggaagtgaacaacagccagaccgaaacccataacgtgtttatgtgcaggaagcgaaatgcg aaaacccggaatttgaacgcaacgtggaaaacaccagctgctttatggtgccgggcgtgctgccggataccctgaacaccgtgcgc attcgcgtgaaaaccaacaacaaactgtgctatgaagatgataaactgtggagcaactggagccaggaaatgagcattggcaaaaaacgc aacagcaccctgtatattaccatgctgattgtgccggtgattgtggcgggcgcgattattgtgctgctgctatctgaaacgcctga aaattattatttttccgccgattccggatccgggcaaaaatttttaaagaaatgtttggcgatcagaacgatgataccctgcattggaaaaaaa tatgatatttatgaaaaacagaccaaagaagaaaccgatagcgtggtgctgattgaaaacctgaaaaaaagcgagccag **(SEQ ID NO: 58)**
IL-10R1	Q13651	Signal peptide removed catgggaccgagctcccagtcctccttctgtttggttcgaagccgaattctttcaccatattctgcactggactcctatcccaaatcaatc agaatcaacatgttacgaggtggcactgctgaggtacggaatcgagtcttggaatagcatttcaaactgtagccaaaccctgtcttacg atcttaccgctgtgacgctggacctgtatcatagcaacggctaccgtgccagggttagggcagttgatggcagcagacactccaattg gacagttacgaatacccgattcagtgtcgacgaggtgacttttaactgtcgggagtgttaaccttgaaattcacaacgggttcatattggg aaagatccagctcccccggccaaaaatggcccccagccaacgacacatacgagagtatatttttctcattttagagagtatgatgagatcgca atccgcaaggtgcctgggaatttcacatttactcatataagaaggtaaaaacacgagaacttctccttgctcacctcgggcgaagtgggggga gttctgcgtgcaggtgaagccctcggtggcttcacgctccaataaaggcatgtggagcaaagaagaatgtatttctctgactcggcagt actttaccgtgactaacgtaatcatatttttttgccttcgtgctcctgctgtctggtgccctggcctattgcctggccgcttcaacttttatgtgcg gaggaggaagaagctgccgtccgtgctgttgtttaagaaaccgtctcccttcatttttatcagccagcgccccctcaccccgaaacacagg atactattcacccccttgacgaagaagccttccttaaagtgtcccccgagctaaaaaacctcgacctgcacgggtccaccgatagcgg gtttggtagccaaaaccatcctgcaaaccgaggagcccccagttcttgctccctgatccacacccacaggctgacagaacgttgggga

		aacagagagcccccagtcctgggggattcctgttcgtcaggtctagtaatagtaccgatagcgggatttgcctgcaggagccgagc ctgtcacctcaaccggtccgacctgggagcagcaagtaggatctaactcccgcgggcaggatgactccggcatagacctcgtaca gaattcggaaggccgggcgggtgacacacaggcggctccgctctgggccaccattcccaccagagcccgaggtccctggcga ggaggacctgcagccgtcgcttttcaaggctatctgcgtcagacacgatgtgctgaagagaaagctactaagacgggatgtcttgaa gaggaatctccgcttacagacggattgggaccaaagttcggcagatgcctagtggatgaggcgggactacatcctcccgcattagca aagggctacctgaagcaggatccactagaaatgacactggcctcatctggcgcccctacaggacagtggaaccagccaaccgaag agtggtccttgctcgctttaagctcttgcagtgacctgggtatctcagattggagttttgcacacgacctcgccccctctgggttgcgtcgc cgctcctggtggactcttaggaagtttcaatagcgatctcgtcactctgcctctcatcagtagcttacagagcagcgaa **(SEQ ID NO: 59)**
IL-10R2	Q08334	Signal peptide removed Atggtaccacccacctgaaaatgtgaggatgaactctgtgaatttaagaacattctccagtgggaaagtcccgctttgctaagggggaa cctgaccttcacagcccaatacttatcctaccgaatcttccaagacaagtgcatgaatataccacttaactgaatgcgacttctcaagcctg tctaagtatggcgatcatacactgcgggttcgtgccgagtttgccgacgagcactctgactgggtgaatataaccttctgccccgtcgat gatactataattgggccaccaggtatgcaagttgaagtgttggcagattcgctgcacatgaggtttctcgcccccaaaatcgagaacga gtacgagacctggacgatgaagaatgtctacaacttggacatataatgttcagtattggaaaaacggaaccgacgagaagtttcaga tcactccgcagtatgatttcgaagtcctgagaaaacctcgagccttggacaacttactgtgtccaagtgcgcggctttctccctgaccgga acaaggcaggagagtggtcagaaccggtgtgtgagcagaccacccacgacgagacagtaccgagctggatggtagctgtgatcctt atggcctccgtgttcatggtttgtctagctttgtgggctgttttgccttctatgtgcgtctataaaaagaccaaatacgcgtttttcaccta gaaacagccttccacagcacctcaaggagttcctgtgggcatcctcatcacaatacactgctgttcttctcctttcccctgagtgacgaaaa acgatgtgtttgataaactgtccgtgattgcagaagacagtgagtccggcaaacagaatccaggagatagttgcagcctgggtacgcc tcccggacagggcccccagagc **(SEQ ID NO: 60)**
IL-18Rα	Q13478	Signal peptide removed gccgagagctgcactagccggcccccatataactgtggtcgaaggggagccattctatctgaaacattgttcctgctcccttgcccatga aattgaaaccacaaccaagagctggtacaaaatctagtgggtctcaagagcacgtcgagttgaacccaagatcatctagtaggatcgcc ctgcatgactgcgttctagagttttggccggtggaatttaaatgacaccggatcttacttcttccagatgaagaattacacccagaaatgga agctgaacgtgatacgacgcaacaagcactcatgcttcacagaacgtcaggtgacctcgaaaatcgtggaagtgaaaaagttctttca gattacatgcgagaacagttactatcaaacgctagtgaatagcacgagcctgtacaaaaactgtaagaaacttctgctggagaacaata aaaaccctactatcaaaaaaaatgcagaattcgaggatcagggctattacagttgtgtgcatttctccaccacaatggtaagctattcaa tatcaccaagacgttcaacatcaccattgtggaggatcgctccaacatagtacctgttattgggtcctaaacttaaccacgtggcagt ggagctgggaaaaacgtgagactcaattgctcagccttgctgaacgaagaggatgttatttattggatgtttgggggaagaaaatgga agtgaccgaacattcacgaagagaagaggatgcgaatcatgacaccagagggggaaatggcacgcgagtaaggtcctcagaattg aaaatattggcgaatcaaatctcaacgtcctctataactgtaccgtagcatccacaggcggcactgatactaagtcctttatccttgtgcgt aaggccgatatggctgacatccccggccacgtattcacacgggggaatgatcattgctgttctgatcctgggtggcagtagtgtgtttggtt

		actgtatgtgttatctaccgcgtggacttagttctgttttataggcacctgacccgaagagacgaaaccccttacagatggcaagacttatg acgcgttcgtgtcgtatcttaaagaatgccggcccgagaatggagaggagcacacgtttgctgtcgaaattctccccagagtcctgga gaagcatttggttacaagctgtgcatcttcgaaagagacgtcgtgccgccgtggtcgacgagatacattccctgatcgag aagtcccgcaggttgatcatagtcctctcaaagtcttacatgagcaatgagtgcggtacgaactcgagagcggactgcatgaggcttt agtcgagaggaagattaagattatttgatcgagtttacacctgtgactgacttacctccctcagtcactgaaactcctaagtctca cagggtactgaagtggaaagctgataaaatcccctcttctataatagccggtttggaagaacctattgtacctgatgccagccaaaacagt caagcctggacgcgatgagcccgaagttctgccagttctgagcgagtcc **(SEQ ID NO: 61)**
IL-18Rβ	O95256	tttaatatctctggatgcagtacgaagaaattgctctggacatactctactaggagcgaggaagagttcgtgctttctgcgatttaccaga accacagaaatcccatttttgtcacagaaatcgtctttctcctaagcaggttcccgaacacctgcccttcatgggctccaacgaccttagt gacgttcaatggtaccagcaaccaagcaatggcgacgcctctggaaagacatacgcaagagttacccccatattatccaggataaatgca cgctacatttcctgacccaggcgtcaacaacagtggatcttatatatgtaggcctaagatgatcaaatcccctacgacgtggcttgtt gcgtcaagatgattctcgaggtgaagccccagaccaatgcctcatgtgagtactccgcctctcacaaacaggaccttctgctgggtc gaccggcagtataagctgcccatcgctctcttgtcagagtgatgcgcagagccctgctgtgacatggtacaaaaaacggaaagctactg tcagtggagcgctcaaaccgtattgtagtagacgaagtctacgactatcaccaaggcacctacgtgtgcgattatacacagtctgatac ggtctccagttggactgtgcgggccgtgtgtgcaggtacggaccatcgtgggggacacaaaactgaagcccgacatccttgatccagt tgaggacaccctggaggtggagctcgggaagcccctgactatctcctgtaaagcaagatttggcttcgagcgagtatttaaccctgtta tcaagtggtatattaaagatagcgatctcgagtgggaggtatcagtgcctgaagccaaatccatcaaatcaactctgaaggatgaaatc attgagcgaaatattattcttgagaaggttacccagcgcgatctccgccgcaaatttgtctgcttcgtgcaaaacagcatagggcaatact actcagagcgtgcagctgaaagagaagcgtggtgtcgtcttgttgtacatcctgctcggaacaattggtacactcgtagccgtgttggc cgcctcagcctgctctacaggcattggattgaaatcgtgttgctttacaggacatatcagagcaaggaccagactctgggcgcacaaa aaggatttcgatgcattcgttagctatgctaaatggtcttcatttcctagcgaaagctacatcctccctgagcgaggaacacttagccttatc actgtttccagatgtgttagaaaataaatatggctatagcctgtgtttgctggagcgcgacgttgcaccaggggggggtgtatgctgaaga catcgtcagcatcatcaagcggtccaggaggggaatatttatattaagccctaactacgtcaacggtccatcgattttcgaactgcaggc tgcagtgaacttggcgctcgatgaccagacgctcaagctgattctcatcaagttctgctactttcaagagcccgagtctcttcctcaccta gtcaagaaggcgctgagagtcctgccgaccgtgacatggcgaggactaaagtctgtgccgccgaattccagattctgggcaaagat gcggtatcatatgcccgttaaaaattcccaaggtttacttggaacccagctgcggattaccagtcggatcttccagtggaaggggctgtc tagaaccgagaccaccggaagatccagtcaacccaaagaatgg **(SEQ ID NO: 62)**	Signal peptide removed

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

Name	Amino Acid Sequence	Notes
scIFN-γ	QDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKD DQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAA SGEFVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFKNFKD DQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAA KTGKRKRSQMLFRG **(SEQ ID NO: 63)**	Single chain; Randal et al 2000
cpIL-1β (89/88)	NYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQF VSSgggggggggggggsAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFV QGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPK **(SEQ ID NO: 64)**	Circular permutation
scIL-12	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGD AGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWL TTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLT FCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGSTSGS GKPGSGEGSTKGRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHED ITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVE FKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLH AFRIRAVTIDRVMSYLNAS **(SEQ ID NO: 65)**	Single chain; p40-linker-p35, Lee et al 2001
cpIL-4 (38-37)	NTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSC PVKEANQSTLENFLERLKTIMREKYSKCSSgggnggHKCDITLQEIIKTLNSLTEQKTLCTELTVTD IFAASK **(SEQ ID NO: 66)**	Circular permutation; Kreitman et al 1994
mIL-10	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGC QALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENGGSGGKS KAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN **(SEQ ID NO: 67)**	Monomeric form; Josephson et al 2000
cpIL-10 (58/57)	GYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSK AVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNggggsgggggsgggsSPGQGTQSENS CTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFK **(SEQ ID NO: 68)**	Circular permutation
tdIL-10	SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGC QALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQV	Tandem-dimer

	KNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNggggsggggsggggsSPGQGTQSENSCTHFP GNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVM PQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKA MSEFDIFINYIEAYMTMKIRN **(SEQ ID NO: 69)**	
cpIL-13 (75/74)	VSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFNggggsLTCLGGFASPGPVPPSTALRE LIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHK **(SEQ ID NO: 70)**	Circular permutation

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

Name	Codon Optimized Sequence	Notes
scIFN-γ	Caggatccctacgtgaaagaagccgagaacttaaagaaatatttcaacgcaggccattcagacgtcgctgataatggaacacttttttgggcattct gaaaaattggaaggaagaatcggaccgaaaaattatgcagagccagatagtatccttttatttcaagttatttaaaaacttcaaagacgatcagtctatc caaaaaagtgtggagactatcaaggaggacatgaatgtgaagttcttcaacagcaataaaaagaaacgggatgactttgaaaagctcaccaattact cagtcactgatctgaacgtgcagagaaaggcgattcatgagctaatccaagtgatggctgagctcggagccaacgtgagcggagagtttgtgaag gaagccgagaatctgaagaagtatttcaacgctggtcactctgacgtggcagataacggcacgctgttcctggggatcctgaagaattggaaagaa gagtccgacaggaagattatgcaatcccagatcgtcagtttctactttaagcttttcaagaatttcaaagacgatcagagtatccagaagtctgtcgag accataaaagaagacatgaatgtaaagtttttttaattcaaacaaaaagaagcgtgacgatttcgaaaaactcaccaactactccgttacagatctgaac gttcagagaaaagccattcacgagttgatccaagttatggccgagctctctcctgcagctaagacaggtaagaggaaacggagccagatgctgttt cgcggg **(SEQ ID NO: 71)**	Single chain; Randal et al 2000
cpIL-1β (89/88)	Aactaccccaaaaaaaagatggagaagcggtttgtttttaacaagattgagatcaacaataagctggaattcgagtctgcgcagttcccaaactggt atattagcacatcgcaagcagaaaatatgcccgtgttcctcggcggaaccaaaggcgggcaggatatcacagactttacgatgcagttcgtgtcatc tggtggtggtggaagcggcgggggaggcagtgggggaggcgggtccgccccagtgaggtccctgaactgtaccttaagagactcacagcaaa agtccctggtcatgtctggcccctacgaactgaaagcccttcacctgcaggggcaagatatggagcagcaggtggttttcagcatgagttttgtaca gggcgaagagagtaatgacaagatacctgtggctctaggactcaaggaaaagaatttgtatctcagctgcgtcctgaaggacgataaacctactctt cagttggagtccgtcgatccgaaa **(SEQ ID NO: 72)**	Circular permutation
scIL-12	atctgggagctcaaaaaggatgtttatgtggtcgaacttgactggtacccggacgcaccaggggagatggtggtgttgacctgcgacacccccga agaggacgggattacatggactttggaccagtccagtgaagtcctgggctcgggaaagaccctgactatccaggtgaaggagttcggagatgctg gacaatatacatgccacaagggcggggaagttttgagccattccctcctgctgctgcataaaaaagaggatggtatttggagcactgatattctgaaa gaccagaaggaacccaagaacaaaacttttctgcggtgtgaggccaagaattacagtggaagattcacctgttggtggttaaccacaatctctaccg	Single Chain; p40-linker-p35, Lee et al 2001

	atcttacctttccgtcaaatcaagtcgcggcagcagcgatccacagggcgtgacgtgcggcgctgccacactaagcgcggagagagtgcgggg tgacaacaaggaatacgagtactccgttgagtgtcaagaagactctgcatgccctgccgcagaggaatcattaccgatcgaagtaatggtggatgc tgttcacaaactgaagtatgaaaactacacttcttcatttttcataagggacattatcaagcctgatcctccaaagaacctccaacttaaaccactcaaga atagccgtcaggtagaggtgtcctgggagtaccccgatacctggtcaacgccccactcatatttctccctgacgttctgtgtgcaggtgcagggaa atccaagagggagaagaaagacagggtctttacagataagacatctgccactgtcatctgcagaaaaaatgcctctatatccgtgcgagcccagga ccgctactattctagtagctggagcgagtgggctagtgtacctttgttcgggctcaaccagcggatccgggaaacccggttctggcgagggggagtac aaagggacgaaatctgccagtggctacccccgacccgggcatgtttccctgcctccatcatagccagaatctgctcagagcggtcagcaacatgct acagaaggcccgccagacctttagagtttaccttgcacctctgaggaaatcgatcacgaagacatcaccaaagataagactagcaccgttgaagc ctgtctcccattggaacttacaaaaaatgaatcttgtctgaattccagagagacatcttttatcactaatggaagttgcctcgccagtcggaaaacttcct tcatgatggccctgtgtctgagttcaatctacgaggatcttaagatgtatcaaagcgatgaacgcaaaactgttgatggatcctaaga ggcagatattttggatcagaacatgttagctgtgatcgacgagctgatgcaagcactcaacttcaactcagagacagtcccccagaagtcctcccctg gaggagcctgacttctacaagacgaaaattaagctatgcattcgcttcacgcattcaggatacgggccgtaacaattgaccgtgtgatgagctatct gaacgcttcg **(SEQ ID NO: 73)**	
cpIL-4 (38-37)	Aatacgactgagaaagagaccttttgtagggctgccacagtcctgcggcagttctatagtcaccatgagaaagacaccagatgtctgggggcaac cgctcagcaattccatagacacaagcagttaatccgatttctgaatcgttgaagcggcttgatcgtaacttgtgggactagccggcctgaactcatgccccgtg aaagaagcgaatcagtccactcttgagaacttcctcgaaaggcttcaagacaattatgcgcgaaaagtacagcaagtgcagctctggcggaaacgg tgggcacaagtgtgatattacgctccaagaaatcatcaagactctgaactcctgaccgagcagaaaacactttgcactgagttgacagtgaccgac atattcgccgctagcaaa **(SEQ ID NO: 74)**	Circular permutation; Kreitman et al 1994
mIL-10	Tcgcctggccagggaacgcagagtgaaaatagctgtacccacttcccggcaacctaccaaatatgctcagagatctgcgggatgcattctcccg ggtgaagacatttttccaaatgaaggatcagttggacaaccttctgttgaaggagtcactcttagaggacttcaagggatacctgggtgccaagcc ctgtctgagatgattcagttctacctcgaagaggtaatgccacaggccgaaaaccaggaccctgatataaaagctcatgtcaatagtttaggcgaga atctgaaaactctcaggctgcgtctgcgaagatgccaccgcttttctgccctgtgagaaccgggggagggtctggtggcaaaagcaaagctgtggag caagttaaaaatgcattcaacaaacttcaggagaaggtatttataaggcgatgtccgaatttgacatctttattaattacatcgaagcctatatgaccat gaagatcaggaac **(SEQ ID NO: 75)**	Monomeric form; Josephson et al 2000
cpIL-10 (58/57)	Ggttacttgggctgtcaggctctgagtgaaatgattcagttctatcttgaagaggttatgcctcaggcggagaaccaagacccagacatcaaggccc atgtgaactctctcgggagaatctgaaaacactgcgactgcggttaagacgttgccacaggttcctaccctgcgaaaataaaagcaaggccgtcg agcaagtgaaaaacgcattcaataaactccaggaaaaggaatttacaaggccatgtccgagtttgatatctttataaactatattgaggcttacatga ccatgaagatccgcaatggtggtgtggaagcggcgggggaggcagtgggggaggcgggtcctcccctggccagggaactcagtcagaaaat agctgcacacacttccagggaatctcccaacatgttgagagatctgagggacgccttctctcgggtgaaaacctttttccaaatgaaagaccagct ggacaacctccttctgaaggagagtttactagaggatttcaag **(SEQ ID NO: 76)**	Circular permutation

tdIL-10	Tctccgggacagggaacccagagcgaaaactcctgcactcattttcctggcaacctccccaatatgctgcgagacttgcgcgacgcattctcaagg gtgaagacgttcttccagatgaaggatcaactggacaacttattgctgaaagaatctctgctcgaggatttcaaaggatacctgggatgtcaggcact gagcgagatgatccaattttacctggaggaggtcatgcctcaggctgagaatcaggatcctgacatcaaggcccacgtgaacagtcttggagaga atcttaagacccttaggctgagacttagacggtgtcaccgctttctgccctgcgaaaataaatcaaaagcggtggaacaggttaagaacgcttttaat aagctgcaggaaaagggcatttataaagctatgagtgaatttgacattttcattaactatatcgaggcctatatgacaatgaaaattaggaacgggggga ggcgggagcgggggcggcggctcaggcggtgggggtcctctccaggtcaaggaacacaatctgagaactcctgcacacacttccccggcaa tctaccaaacatgctcagagatctcagggacgcgttcagtcgagtgaaaactttcttccagatgaaggatcagctggacaatctactgctgaaagaa agcttgcttgaggattttaaaggctatctgggttgtcaggccttatcggagatgatccagttttacttggaggaagttatgcctcaggcagaaaaccaa gaccccgatatcaaggctcatgtgaattccctcggtgaaaacctaaagaccttacgcctgcgtctcagacggtgtcatcggtttttgccatgcgagaa taagtccaaagccgtagagcaggtcaagaatgccttcaataagctccaggagaaggggatatacaaagcaatgagcgaatttgacattttcatcaac tacatagaggcctacatgaccatgaagatccggaac **(SEQ ID NO: 77)**	Tandem-dimer
cpIL-13 (75/74)	Gtgagcgcgggccagtttagcagcctgcatgtgcgcgataccaaaattgaagtggcgcagtttgtgaaagatctgctgctgcatctgaaaaaactg tttcgcgaaggccgctttaacggaggaggtggatctctgacctgcctgggcggctttgcgagcccgggcccggtgccgccgagcaccgcgctgc gcgaactgattgaagaactggtgaacattacccagaaccagaaagcgccgctgtgcaacggcagcatggtgtggagcattaacctgaccgcggg catgtattgcgcggcgctggaaagcctgattaacgtgagcggctgcagcgcgattgaaaaaacccagcgcatgctgagcggcttttgcccgcata aa **(SEQ ID NO: 78)**	Circular permutation

Table 8 – Sequences of Linkers and Signal Peptide

Name	Amino Acid Sequence	Codon Optimized
(G4S)3 linker	GGGGSGGGGSGGGGS	Ggtggtggtggaagcggcgggggaggcagtgggggaggcgggtcc **(SEQ ID NO: 79)**
Whitlow linker	GSTSGSGKPGSGEGSTKG	Ggctcaaccagcggatccgggaaacccggttctggcgaggggagtacaaaggga **(SEQ ID NO: 80)**
Linker 26	SGGGSGGGGSGGGGSGGGGSGGGSLQ	Tctggaggcggaagcgggggtggcggcagcggcggtggaggatcaggtggcgggggggtccgggggcggaagtctgcag **(SEQ ID NO: 81)**
CD8a signal peptide	MALPVTALLLPLALLLHAARP	ATGGCCTTGCCTGTGACCGCATTACTGCTTCCACTCGCCCTGCTCCTGCACGCTGCGAGACCC **(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	MALPVTALLLPLALLLHAARPCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQ KAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSIL AVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKESGGGSGGGGSGGGGSGGGGS GGGSLQKNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNITSTKCNFS SLKLNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEAEDKAIVIHISPGTKDSVMWALDG LSFTYSLVIWKNSSGVEERIENIYSRHKIYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVENELPP PENIEVSVQNQNYVLKWDYTYANMTFQVQWLHAFLKRNPGNHLYKWKQIPDCENVKTTQCVFPQNV FQKGIYLLRVQASDGNNTSFWSEEIKFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQSGNTPVIQDYPLIY EIIFWENTSNAERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFSDAVCEKTKPGNTSKIW LIVGICIALFALPFVIYAAKVFLRCINYVFFPSLKPSSSIDEYFSEQPLKNLLLSTSEEQIEKCFIIENISTIATV EETNQTDEDHKKYSSQTSQDSGNYSNEDESESKTSEELQQDFV **(SEQ ID NO: 83)**
IFN-α2	IFNAR2	MALPVTALLLPLALLLHAARPCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQ KAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSIL AVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKESGGGSGGGGSGGGGSGGGGS GGGSLQISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNCANTTRS FCDLTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPEFEIVGFTNHINVMVKFPSIVEEE LQFDLSLVIEEQSEGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTLLPP GQESESAESAKIGGIITVFLIALVLTSTIVTLKWIGYICLRNSLPKVLNFHNFLAWPFPNLPPLEAMDMVE VIYINRKKKVWDYNYDDESDSDTEAAPRTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEEPDLPE VDVELPTMPKDSPQQLELLSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFNVDLNSVFLRVLDDEDSD DLEAPLMLSSHLEEMVDPEDPDNVQSNHLLASGEGTQPTFPSPSSEGLWSEDAPSDQSDTSESDVDLGD GYIMR **(SEQ ID NO: 84)**
IFN-β	IFNAR1	MALPVTALLLPLALLLHAARPMSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQL QQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKL MSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRNSGGGSGGGGSGGGGSGGG GSGGGSLQKNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFDYQKTGMDNWIKLSGCQNITSTKC NFSSLKLNVYEEIKLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEAEDKAIVIHISPGTKDSVMWA

		LDGLSFTYSLVIWKNSSGVEERIENIYSRHKIYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVEN ELPPPENIEVSVQNQNYVLKWDYTYANMTFQVQWLHAFLKRNPGNHLYKWKQIPDCENVKTTQCVFP QNVFQKGIYLLRVQASDGNNTSFWSEEIKFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQSGNTPVIQDY PLIYEIIFWENTSNAERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLNKSSVFSDAVCEKTKPGNTS KIWLIVGICIALFALPFVIYAAKVFLRCINYVFFPSLKPSSSIDEYFSEQPLKNLLLSTSEEQIEKCFIIENIST IATVEETNQTDEDHKKYSSQTSQDSGNYSNEDESESKTSEELQQDFV **(SEQ ID NO: 85)**
IFN-β	IFNAR2	MALPVTALLLPLALLLHAARPMSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQL QQFQKEDAALTIYEMLQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKL MSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRNSGGGSGGGGSGGGGSGGG GSGGGSLQISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDLKVVKNCANT TRSFCDLTDEWRSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPEFEIVGFTNHINVMVKFPSIV EEELQFDLSLVIEEQSEGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTL LPPGQESESAESAKIGGIITVFLIALVLTSTIVTLKWIGYICLRNSLPKVLNFHNFLAWPFPNLPPLEAMDM VEVIYINRKKKVWDYNYDDESDSDTEAAPRTSGGGYTMHGLTVRPLGQASATSTESQLIDPESEEEPDL PEVDVELPTMPKDSPQQLELLSGPCERRKSPLQDPFPEEDYSSTEGSGGRITFNVDLNSVFLRVLDDEDS DDLEAPLMLSSHLEEMVDPEDPDNVQSNHLLASGEGTQPTFPSPSSEGLWSEDAPSDQSDTSESDVDLG DGYIMR **(SEQ ID NO: 86)**
IFN-γ	IFNGR1	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQ SQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQ VMAELSPAAKTGKRKRSQMLFRGSGGGSGGGGSGGGGSGGGSLQEMGTADLGPSSVPTPTN VTIESYNMNPIVYWEYQIMPQVPVFTVEVKNYGVKNSEWIDACINISHHYCNISDHVGDPSNSLWVRV KARVGQKESAYAKSEEFAVCRDGKIGPPKLDIRKEEKQIMIDIFHPSVFVNGDEQEVDYDPETTCYIRVY NVYVRMNGSEIQYKILTQKEDDCDEIQCQLAIPVSSLNSQYCVSAEGVLHVWGVTTEKSKEVCITIFNS SIKGSLWIPVVAALLLFLVLSLVFICFYIKKINPLKEKSIILPKSLISVVRSATLETKPESKYVSLITSYQPFSL EKEVVCEEPLSPATVPGMHTEDNPGKVEHTEELSSITEVVTTEENIPDVVPGSHLTPIERESSSPLSSNQSE PGSIALNSYHSRNCSESDHSRNGFDTDSSCLESHSSLSDSEFPPNNKGEIKTEGQELITVIKAPTSFGYDK PHVLVDLLVDDSGKESLIGYRPTEDSKEFS **(SEQ ID NO: 87)**
IFN-γ	IFNGR2	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQ SQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQ VMAELSPAAKTGKRKRSQMLFRGSGGGSGGGGSGGGGSGGGSLQAPPDPLSQLPAPQHPKIR LYNAEQVLSWEPVALSNSTRPVVYQVQFKYTDSKWFTADIMSIGVNCTQITATECDFTAASPSAGFPMD

		FNVTLRLRAELGALHSAWVTMPWFQHYRNVTVGPPENIEVTPGEGSLIIRFSSPFDIADTSTAFFCYYVH YWEKGGIQQVKGPFRSNSISLDNLKPSRVYCLQVQAQLLWNKSNIFRVGHLSNISCYETMADASTELQ QVILISVGTFSLLSVLAGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPTQPILEALDKDSSPKDDVW DSVSIISFPEKEQEDVLQTL **(SEQ ID NO: 88)**
scIFN-γ	IFNGR1	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQ SQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQ VMAELGANVSGEFVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFK NFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAAKT GKRKRSQMLFRGSGGGSGGGGSGGGGSGGGSLQEMGTADLGPSSVPTPTNVTIESYNMNPIV YWEYQIMPQVPVFTVEVKNYGVKNSEWIDACINISHHYCNISDHVGDPSNSLWVRVKARVGQKESAY AKSEEFAVCRDGKIGPPKLDIRKEEKQIMIDIFHPSVFVNGDEQEVDYDPETTCYIRVYNVYVRMNGSEI QYKILTQKEDDCDEIQCQLAIPVSSLNSQYCVSAEGVLHVWGVTTEKSKEVCITIFNSSIKGSLWIPVVA ALLLFLVLSLVFICFYIKKINPLKEKSIILPKSLISVVRSATLETKPESKYVSLITSYQPFSLEKEVVCEEPLS PATVPGMHTEDNPGKVEHTEELSSITEVVTTEENIPDVVPGSHLTPIERESSSPLSSNQSEPGSIALNSYHS RNCSESDHSRNGFDTDSSCLESHSSLSDSEFPPNNKGEIKTEGQELITVIKAPTSFGYDKPHVLVDLLVD DSGKESLIGYRPTEDSKEFS **(SEQ ID NO: 89)**
scIFN-γ	IFNGR2	MALPVTALLLPLALLLHAARPQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQ SQIVSFYFKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQ VMAELGANVSGEFVKEAENLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIMQSQIVSFYFKLFK NFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLTNYSVTDLNVQRKAIHELIQVMAELSPAAKT GKRKRSQMLFRGSGGGSGGGGSGGGGSGGGSLQAPPDPLSQLPAPQHPKIRLYNAEQVLSWE PVALSNSTRPVVYQVQFKYTDSKWFTADIMSIGVNCTQITATECDFTAASPSAGFPMDFNVTLRLRAEL GALHSAWVTMPWFQHYRNVTVGPPENIEVTPGEGSLIIRFSSPFDIADTSTAFFCYYVHYWEKGGIQQV KGPFRSNSISLDNLKPSRVYCLQVQAQLLWNKSNIFRVGHLSNISCYETMADASTELQQVILISVGTFSL LSVLAGACFFLVLKYRGLIKYWFHTPPSIPLQIEEYLKDPTQPILEALDKDSSPKDDVWDSVSIISFPEKE QEDVLQTL **(SEQ ID NO: 90)**
TNF-α	TNFR1	MALPVTALLLPLALLLHAARPVRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDN QLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYE PIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALSGGGSGGGGSGGGGSGGGSLQLV PHLGDREKRDSVCPQGKYIHPQNNSICCTKCHKGTYLYNDCPGPGQDTDCRECESGSFTASENHLRHC LSCSKCRKEMGQVEISSCTVDRDTVCGCRKNQYRHYWSENLFQCFNCSLCLNGTVHLSCQEKQNTVC

		TCHAGFFLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDSGTTVLLPLVIFFGLCLLSLLFIGLMYRY QRWKSKLYSIVCGKSTPEKEGELEGTTTKPLAPNPSFSPTPGFTPTLGFSPVPSSTFTSSSTYTPGDCPNFA APRREVAPPYQGADPILATALASDPIPNPLQKWEDSAHKPQSLDTDDPATLYAVVENVPPLRWKEFVRR LGLSDHEIDRLELQNGRCLREAQYSMLATWRRRTPRREATLELLGRVLRDMDLLGCLEDIEEALCGPA ALPPAPSLLR **(SEQ ID NO: 91)**
TNF-α	TNFR2	MALPVTALLLPLALLLHAARPVRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDN QLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYE PIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALSGGGSGGGGSGGGGSGGGGSLQLP AQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWNWVP ECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGTETSDV VCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPVSTRSQHTQP TPEPSTAPSTSFLLPMGPSPPAEGSTGDFALPVGLIVGVTALGLLIIGVVNCVIMTQVKKKPLCLQREAKV PHLPADKARGTQGPEQQHLLITAPSSSSSSLESSASALDRRAPTRNQPQAPGVEASGAGEARASTGSSDS SPGGHGTQVNVTCIVNVCSSSDHSSQCSSQASSTMGDTDSSPSESPKDEQVPFSKEECAFRSQLETPETL LGSTEEKPLPLGVPDAGMKPS **(SEQ ID NO: 92)**
IL-1β	IL-1R1	MALPVTALLLPLALLLHAARPAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSF VQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESA QFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSSGGGSGGGGSGGGSGGGSLQLEA DKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIIHQHKEKLWFVPAKVE DSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPK LQWYKDCKPLLLDNIHFSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRP VIVSPANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITV LNISEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCSVFIYKIFKIDIVLWYR DSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEKQCGYKLFIYGRDDYVGEDIVE VINENVKKSRRLIIILVRETSGFSWLGGSSEEQIAMYNALVQDGIKVVLLELEKIQDYEKMPESIKFIKQK HGAIRWSGDFTQGPQSAKTRFWKNVRYHMPVQRRSPSSKHQLLSPATKEKLQREAHVPLG **(SEQ ID NO: 93)**
IL-1β	IL-1R3	MALPVTALLLPLALLLHAARPAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSF VQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESA QFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSSSGGGSGGGGSGGGSGGGSLQSER CDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLIWYWTRQDRDLEEPINFRLPENRIS

		KEKDVLWFRPTLLNDTGNYTCMLRNTTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPN VDGYFPSSVKPTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTV KVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTINES ISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPRYTVELACGFGATVLL VVILIVVYHVVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAEEEEFVLLTLRGVLENEFGYKLCI FDRDSLPGGIVTDETLSFIQKSRRLLVVLSPNYVLQGTQALLELKAGLENMASRGNINVILVQYKAVKE TKVKELKRAKTVLTVIKWKGEKSKYPQGRFWKQLQVAMPVKKSPRRSSSDEQGLSYSSLKNV **(SEQ ID NO: 94)**
cpIL-1β (89/88)	IL-1R1	MALPVTALLLPLALLLHAARPNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVFLG GTKGGQDITDFTMQFVSSGGGGSGGGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQ DMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKSGGGSGGGSGGG GSGGGGSGGGSLQLEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRI HQHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKLPVAGDGGLVC PYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPI TRVIEFITLEENKPTRPVIVSPANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYY SVENPANKRRSTLITVLNISEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCS VFIYKIFKIDIVLWYRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDIFVFKVLPEVLEKQCGYKL FIYGRDDYVGEDIVEVINENVKKSRRLIIILVRETSGFSWLGGSSEEQIAMYNALVQDGIKVVLLELEKIQ DYEKMPESIKFIKQKHGAIRWSGDFTQGPQSAKTRFWKNVRYHMPVQRRSPSSKHQLLSPATKEKLQR EAHVPLG **(SEQ ID NO: 95)**
cpIL-1β (89/88)	IL-1R3	MALPVTALLLPLALLLHAARPNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVFLG GTKGGQDITDFTMQFVSSGGGGSGGGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQ DMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKSGGGSGGGSGGG GSGGGGSGGGSLQSERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLIWYWTRQ DRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRNTTYCSKVAFPLEVVQKDSCFNSPMKL PVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVV TYPENGRTFHLTRTLTVKVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWT IDGKKPDDITIDVTINESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAP RYTVELACGFGATVLLVVILIVVYHVVYWLEMVLFYRAHFGTDETILDGKEYDIYVSYARNAEEEEFVLL TLRGVLENEFGYKLCIFDRDSLPGGIVTDETLSFIQKSRRLLVVLSPNYVLQGTQALLELKAGLENMAS

		RGNINVILVQYKAVKETKVKELKRAKTVLTVIKWKGEKSKYPQGRFWKQLQVAMPVKKSPRRSSSDE QGLSYSSLKNV **(SEQ ID NO: 96)**
IL-6	IL-6Rα	MALPVTALLLPLALLLHAARPVPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMC ESSKEALAENNLNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMST KVLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKEFLQSSLRALRQMSGG GSGGGGSGGGGSGGGGSLQLAPRRCPAQEVARGVLTSLPGDSVTLTCPGVEPEDNATVHWVLR KPAAGSHPSRWAGMGRRLLLRSVQLHDSGNYSCYRAGRPAGTVHLLVDVPPEEPQLSCFRKSPLSNVV CEWGPRSTPSLTTKAVLLVRKFQNSPAEDFQEPCQYSQESQKFSCQLAVPEGDSSFYIVSMCVASSVGSK FSKTQTFQGCGILQPDPPANITVTAVARNPRWLSVTWQDPHSWNSSFYRLRFELRYRAERSKTFTTWMV KDLQHHCVIHDAWSGLRHVVQLRAQEEFGQGEWSEWSPEAMGTPWTESRSPPAENEVSTPMQALTTN KDDDNILFRDSANATSLPVQDSSSVPLPTFLVAGGSLAFGTLLCIAIVLRFKKTWKLRALKEGKTSMHPP YSLGQLVPERPRPTPVLVPLISPPVVSPSSLGSDNTSSHNRPDARDPRSPYDISNTDYFFPR **(SEQ ID NO: 97)**
IL-6	gp130	MALPVTALLLPLALLLHAARPVPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMC ESSKEALAENNLNLPKMAEKDGCFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMST KVLIQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKEFLQSSLRALRQMSGG GSGGGGSGGGGSGGGGSLQELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIV WKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEG KKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALG KVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDT ASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRT VQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL TIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTY LRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWDQLPVDVQNG FIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEA IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFT DVSVVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYS TVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDIS HFERSKQVSSVNEEDFVRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEAAT DEGMPKSYLPQTVRQGGYMPQ **(SEQ ID NO: 98)**

scIL-12	IL-12-Rβ1	MALPVTALLLPLALLLHAARPIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEV
		LGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNY
		SGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEES
		LPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCV
		QVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGSTSGSGKPGSGEGST
		KGRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLE
		LTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQN
		MLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASSGGGSGGGG
		SGGGGSGGGGSGGGSLQCRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYECSWQYEGPTAGVS
		HFLRCCLSSGRCCYFAAGSATRLQFSDQAGVSVLYTVTLWVESWARNQTEKSPEVTLQLYNSVKYEPP
		LGDIKVSKLAGQLRMEWETPDNQVGAEVQFRHRTPSSPWKLGDCGPQDDDTESCLCPLEMNVAQEFQ
		LRRRQLGSQGSSWSKWSSPVCVPPENPPQPQVRFSVEQLGQDGRRRLTLKEQPTQLELPEGCQGLAPG
		TEVTYRLQLHMLSCPCKAKATRTLHLGKMPYLSGAAYNVAVISSNQFGPGLNQTWHIPADTHTEPVAL
		NISVGTNGTTMYWPARAQSMTYCIEWQPVGQDGGLATCSLTAPQDPDPAGMATYSWSRESGAMGQE
		KCYYITIFASAHPEKLTLWSTVLSTYHFGGNASAAGTPHHVSVKNHSLDSVSVDWAPSLLSTCPGVLKE
		YVVRCRDEDSKQVSEHPVQPTETQVTLSGLRAGVAYTVQVRADTAWLRGVWSQPQRFSIEVQVSDWL
		IFFASLGSFLSILLVGVLGYLGLNRAARHLCPPLPTPCASSAIEFPGGKETWQWINPVDFQEEASLQEALV
		VEMSWDKGERTEPLEKTELPEGAPELALDTELSLEDGDRCKAKM **(SEQ ID NO: 99)**
scIL-12	IL-12-Rβ2	MALPVTALLLPLALLLHAARPIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEV
		LGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNY
		SGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEES
		LPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCV
		QVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGSTSGSGKPGSGEGST
		KGRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLE
		LTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQN
		MLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASSGGGSGGGG
		SGGGGSGGGGSGGGSLQKIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFHYSRRNKLILYKFDR
		RINFHHGHSLNSQVTGLPLGTTLFVCKLACINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQGTVACTW
		ERGRDTHLYTEYTLQLSGPKNLTWQKQCKDIYCDYLDFGINLTPESPESNFTAKVTAVNSLGSSSSLPST
		FTFLDIVRPLPPWDIRIKFQKASVSRCTLYWRDEGLVLLNRLRYRPSNSRLWNMVNVTKAKGRHDLLD
		LKPFTEYEFQISSKLHLYKGSWSDWSESLRAQTPEEEPTGMLDVWYMKRHIDYSRQQISLFWKNLSVS
		EARGKILHYQVTLQELTGGKAMTQNITGHTSWTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAG

		LLAPRQVSANSEGMDNILVTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNWLRSRPYNVSALISEN IKSYICYEIRVYALSGDQGGCSSILGNSKHKAPLSGPHINAITEEKGSILISWNSIPVQEQMGCLLHYRIY WKERDSNSQPQLCEIPYRVSQNSHPINSLQPRVTYVLWMTALTAAGESSHGNEREFCLQGKANWMAFV APSICIAIIMVGIFSTHYFQQKVFVLLAALRPQWCSREIPDPANSTCAKKYPIAEEKTQLPLDRLLIDWPT PEDPEPLVISEVLHQVTPVFRHPPCSNWPQREKGIQGHQASEKDMMHSASSPPPPRALQAESRQLVDLY KVLESRGSDPKPENPACPWTVLPAGDLPTHDGYLPSNIDDLPSHEAPLADSLEELEPQHISLSVFPSSSLH PLTFSCGDKLTLDQLKMRCDSLML **(SEQ ID NO: 100)**
IL-4	IL-4Rα	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTEKETFCRAAT VLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKT IMREKYSKCSSSGGGSGGGSGGGSGGGSGGGSLQMKVLQEPTCVSDYMSISTCEWKMNGPTNCS TELRLLYQLVFLLSEAHTCIPENNGGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVK PRAPGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLK SGISYRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKE WWDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLLPCFLEHNMKRDEDPHKAAK EMPFQGSGKSAWCPVEISKTVLWPESISVVRCVELFEAPVECEEEEVEEEKGSFCASPESSRDDFQEGR EGIVARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPWGKEQPLHLE PSPPASPTQSPDNLTCTETPLVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPT TVPQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGLGPPGEAGYKAFSS LLASSAVSPEKCGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLG LEPGEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQTPVMASPCCGCC CGDRSSPPTTPLRAPDPSPGGVPLEASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGP TYMRVS **(SEQ ID NO: 101)**
IL-4	IL-2R*γc*	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTEKETFCRAAT VLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKT IMREKYSKCSSSGGGSGGGSGGGSGGGSGGGSLQLNTTILTPNGNEDTTADFFLTTMPTDSLSVST LPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQKKEI HLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFLNHCLEHLVQYR TDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENPFL FALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVSKGLAESLQPDYSE RLCLVSEIPPKGGALGEGPGASPCNQHSPYWAPPCYTLKPET **(SEQ ID NO: 102)**

IL-4	IL-13Rα1	MALPVTALLLPLALLLHAARPHKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTEKETFCRAAT VLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKT IMREKYSKCSSSGGGSGGGSGGGGSGGGGSLQGGGGAAPTETQPPVTNLSVSVENLCTVIWT WNPPEGASSNCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPE GDPESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFGCSFDLT KVKDSSFEQHSVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFY EVEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNTVRIRVKTNKLCYEDDKLW SNWSQEMSIGKKRNSTLYITMLLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHW KKYDIYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 103)**
cpIL-4 (38-37)	IL-4Rα	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLK RLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTE QKTLCTELTVTDIFAASKSGGGSGGGSGGGGSGGGGSLQMKVLQEPTCVSDYMSISTCEWKM NGPTNCSTELRLLYQLVFLLSEAHTCIPENNGGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSF KPSEHVKPRAPGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSL RIAASTLKSGISYRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYV SITKIKKEWWDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLLPCFLEHNMKRDE DPHKAAKEMPFQGSGKSAWCPVEISKTVLWPESISVVRCVELFEAPVECEEEEEVEEEKGSFCASPESS RDDFQEGREGIVARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPW GKEQPLHLEPSPPASPTQSPDNLTCTETPLVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEM PCVPQLSEPTTVPQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGLGPP GEAGYKAFSSLLASSAVSPEKCGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSS HLPSSSPEHLGLEPGEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQTP VMASPCCGCCCGDRSSPPTTPLRAPDPSPGGVPLEASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQT PKIVNFVSVGPTYMRVS **(SEQ ID NO: 104)**
cpIL-4 (38-37)	IL-2Rγc	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLK RLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTE QKTLCTELTVTDIFAASKSGGGSGGGSGGGGSGGGGSLQLNTTILTPNGNEDTTADFFLTTMPT DSLSVSTLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGC QLQKKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFLNHCL EHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNT

		SKENPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVSKGLAES LQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSPYWAPPCYTLKPET **(SEQ ID NO: 105)**
cpIL-4 (38-37)	IL-13Ra1	MALPVTALLLPLALLLHAARPNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLK RLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKCSSGGNGGHKCDITLQEIIKTLNSLTE QKTLCTELTVTDIFAASKSGGGSGGGGSGGGGSGGGGSLQGGGGAAPTETQPPVTNLSVSVENL CTVIWTWNPPEGASSNCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVE KCISPPEGDPESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFG CSFDLTKVKDSSFEQHSVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFI SRCLFYEVEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNTVRIRVKTNKLCYE DDKLWSNWSQEMSIGKKRNSTLYITMLLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQND DTLHWKKYDIYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 106)**
IL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGGSGGGGSGG GSLQHGTELPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSISNCSQTLSYDLTAVTL DLYHSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHNGFILGKIQLPRPKMAPANDT YESIFSHFREYEIAIRKVPGNFTFTHKKVKHENFSLLTSGEVGEFCVQVKPSVASRSNKGMWSKEECISL TRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYVRRRKKLPSVLLFKKPSPFIFISQRPSPETQDTIHPLDE EAFLKVSPELKNLDLHGSTDSGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPPVLGDSCSSGSSNST DSGICLQEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSALGHHSPPEPEVPGEED PAAVAFQGYLRQTRCAEEKATKTGCLEEESPLTDGLGPKFGRCLVDEAGLHPPALAKGYLKQDPLEMT LASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSFAHDLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQ SSE **(SEQ ID NO: 107)**
IL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGGSGGGGSGG GSLQMVPPPENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMNTTLTECDFSSLSKYG DHTLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLAPKIENEYETWTMKNVYNS WTYNVQYWKNGTDEKFQITPQYDFEVLRNLEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQTTHDET VPSWMVAVILMASVFMVCLALLGCFALLWCVYKKTKYAFSPRNSLPQHLKEFLGHPHHNTLLFFSFPL SDENDVFDKLSVIAEDSESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 108)**

mIL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NGGGSGGGKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGGSGG GGGSGGGSLQHGTELPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSISNCSQTLSY DLTAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHNGFILGKIQLPRPKM APANDTYESIFSHFREYEIAIRKVPGNFTFTHKKVKHENFSLLTSGEVGEFCVQVKPSVASRSNKGMWS KEECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYVRRRKKLPSVLLFKKPSPFIFISQRPSPETQD TIHPLDEEAFLKVSPELKNLDLHGSTDSGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPPVLGDSCS SGSSNSTDSGICLQEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSALGHHSPPEP EVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEESPLTDGLGPKFGRCLVDEAGLHPPALAKGYLK QDPLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSFAHDLAPLGCVAAPGGLLGSFNSDLV TLPLISSLQSSE **(SEQ ID NO: 109)**
mIL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NGGGSGGGKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSGGGSGGGGSGG GGGSGGGSLQMVPPPENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMNTTLTECDFS SLSKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLAPKIENEYETWTM KNVYNSWTYNVQYWKNGTDEKFQITPQYDFEVLRNLEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQ TTHDETVPSWMVAVILMASVFMVCLALLGCFALLWCVYKKTKYAFSPRNSLPQHLKEFLGHPHHNTL LFFSFPLSDENDVFDKLSVIAEDSESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 110)**
cpIL-10 (58/57)	IL-10R1	MALPVTALLLPLALLLHAARPGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLR LRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGSGGGSGG GGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKSGGGSGGG GSGGGGSGGGGSGGSLQHGTELPSPPSVWFEAEFFHHILHWTPIPNQSESTCYEVALLRYGIESWNSIS NCSQTLSYDLTAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGSVNLEIHNGFILGK IQLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTHKKVKHENFSLLTSGEVGEFCVQVKPSVASRS NKGMWSKEECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQLYVRRRKKLPSVLLFKKPSPFIFISQR PSPETQDTIHPLDEEAFLKVSPELKNLDLHGSTDSGFGSTKPSLQTEEPQFLLPDPHPQADRTLGNREPP VLGDSCSSGSSNSTDSGICLQEPSLSPSTGPTWEQQVGSNSRGQDDSGIDLVQNSEGRAGDTQGGSALG HHSPPEPEVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEESPLTDGLGPKFGRCLVDEAGLHPPAL

		AKGYLKQDPLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGISDWSFAHDLAPLGCVAAPGGLLGS FNSDLVTLPLISSLQSSE **(SEQ ID NO: 111)**
cpIL-10 (58/57)	IL-10R2	MALPVTALLLPLALLLHAARPGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLR LRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGG GGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKSGGGSGGG GSGGGGSGGGGSGGGSLQMVPPPENVRMNSVNFKNILQWESPAFAKGNLTFTAQYLSYRIFQDKCMN TTLTECDFSSLSKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIGPPGMQVEVLADSLHMRFLAPKIE NEYETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDFEVLRNLEPWTTYCVQVRGFLPDRNKAG EWSEPVCEQTTHDETVPSWMVAVILMASVFMVCLALLGCFALLWCVYKKTKYAFSPRNSLPQHLKEF LGHPHHNTLLFFSFPLSDENDVFDKLSVIAEDSESGKQNPGDSCSLGTPPGQGPQS **(SEQ ID NO: 112)**
tdIL-10	IL-10R1	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGGGGSSPGQGTQS ENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEV MPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEF DIFINYIEAYMTMKIRNSGGSGGGGSGGGGSGGGSLQHGTELPSPPSVWFEAEFFHHILHWTP IPNQSESTCYEVALLRYGIESWNSISNCSQTLSYDLTAVTLDLYHSNGYRARVRAVDGSRHSNWTVTNT RFSVDEVTLTVGSVNLEIHNGFILGKIQLPRPKMAPANDTYESIFSHFREYEIAIRKVPGNFTFTHKKVKH ENFSLLTSGEVGEFCVQVKPSVASRSNKGMWSKEECISLTRQYFTVTNVIIFFAFVLLLSGALAYCLALQ LYVRRRKKLPSVLLFKKPSPFIFISQRPSPETQDTIHPLDEEAFLKVSPELKNLDLHGSTDSGFGSTKPSLQ TEEPQFLLPDPHPQADRTLGNREPPVLGDSCSSGSSNSTDSGICLQEPSLSPSTGPTWEQQVGSNSRGQD DSGIDLVQNSEGRAGDTQGGSALGHHSPPEPEVPGEEDPAAVAFQGYLRQTRCAEEKATKTGCLEEESP LTDGLGPKFGRCLVDEAGLHPPALAKGYLKQDPLEMTLASSGAPTGQWNQPTEEWSLLALSSCSDLGI SDWSFAHDLAPLGCVAAPGGLLGSFNSDLVTLPLISSLQSSE **(SEQ ID NO: 113)**
tdIL-10	IL-10R2	MALPVTALLLPLALLLHAARPSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLL LKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCE NKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGGGGSSPGQGTQS ENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEV MPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKLQEKGIYKAMSEF DIFINYIEAYMTMKIRNSGGSGGGGSGGGGSGGGSLQMVPPPENVRMNSVNFKNILQWESPA FAKGNLTFTAQYLSYRIFQDKCMNTTLTECDFSSLSKYGDHTLRVRAEFADEHSDWVNITFCPVDDTIIG

		PPGMQVEVLADSLHMRFLAPKIENEYETWTMKNVYNSWTYNVQYWKNGTDEKFQITPQYDFEVLRN LEPWTTYCVQVRGFLPDRNKAGEWSEPVCEQTTHDETVPSWMVAVILMASVFMVCLALLGCFALLW CVYKKTKYAFSPRNSLPQHLKEFLGHPHHNTLLFFSFPLSDENDVFDKLSVIAEDSESGKQNPGDSCSL GTPPGQGPQS **(SEQ ID NO: 114)**
IL-13	IL-13Ra1	MALPVTALLLPLALLLHAARPLTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLT AGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFRE GRFNSGGGSGGGGSGGGGSGGGGSLQGGGGAAPTETQPPVTNLSVSVENLCTVIWTWNPPEGA SSNCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEGDPESAVT ELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFGCSFDLTKVKDSSFE QHSVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFYEVEVNNS QTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNTVRIRVKTNKLCYEDDKLWSNWSQEM SIGKKRNSTLYITMLLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWKKYDIYE KQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 115)**
IL-13	IL-4Ra	MALPVTALLLPLALLLHAARPLTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLT AGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFRE GRFNSGGGSGGGGSGGGGSGGGGSLQMKVLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLY QLVFLLSEAHTCIPENNGGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPRAPGNL TVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLKSGISYRA RVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKEWWDQIP NPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLLPCFLEHNMKRDEDPHKAAKEMPFQG SGKSAWCPVEISKTVLWPESISVVRCVELFEAPVECEEEEVEEEKGSFCASPESSRDDFQEGREGIVAR LTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPWGKEQPLHLEPSPPAS PTQSPDNLTCTETPLVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTTVPQP EPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGLGPPGEAGYKAFSSLLASS AVSPEKCGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLGLEPGE KVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQTPVMASPCCGCCCGDR SSPPTTPLRAPDPSPGGVPLEASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPTYMR VS **(SEQ ID NO: 116)**
cpIL-13 (75/74)	IL-13Ra1	MALPVTALLLPLALLLHAARPVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFNGGGGSLTCL GGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQR MLSGFCPHKSGGGSGGGGSGGGGSGGGGSLQGGGGAAPTETQPPVTNLSVSVENLCTVIWTW

		NPPEGASSNCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGSQCSTNESEKPSILVEKCISPPEG DPESAVTELQCIWHNLSYMKCSWLPGRNTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFGCSFDLTK VKDSSFEQHSVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENPQNFISRCLFYE VEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVPGVLPDTLNTVRIRVKTNKLCYEDDKLWS NWSQEMSIGKKRNSTLYITMLLIVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWK KYDIYEKQTKEETDSVVLIENLKKASQ **(SEQ ID NO: 117)**
cpIL-13 (75/74)	IL-4Ra	MALPVTALLLPLALLLHAARPVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFNGGGGSLTCL GGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQR MLSGFCPHKSGGGSGGGGSGGGGSGGGGSLQMKVLQEPTCVSDYMSISTCEWKMNGPTNCST ELRLLYQLVFLLSEAHTCIPENNGGAGCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKP RAPGNLTVHTNVSDTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLKS GISYRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQHLLLGVSVSCIVILAVCLLCYVSITKIKKEW WDQIPNPARSRLVAIIIQDAQGSQWEKRSRGQEPAKCPHWKNCLTKLLPCFLEHNMKRDEDPHKAAKE MPFQGSGKSAWCPVEISKTVLWPESISVVRCVELFEAPVECEEEEVEEEKGSFCASPESSRDDFQEGRE GIVARLTESLFLDLLGEENGGFCQQDMGESCLLPPSGSTSAHMPWDEFPSAGPKEAPPWGKEQPLHLEP SPPASPTQSPDNLTCTETPLVIAGNPAYRSFSNSLSQSPCPRELGPDPLLARHLEEVEPEMPCVPQLSEPTT VPQPEPETWEQILRRNVLQHGAAAAPVSAPTSGYQEFVHAVEQGGTQASAVVGLGPPGEAGYKAFSSL LASSAVSPEKCGFGASSGEEGYKPFQDLIPGCPGDPAPVPVPLFTFGLDREPPRSPQSSHLPSSSPEHLGL EPGEKVEDMPKPPLPQEQATDPLVDSLGSGIVYSALTCHLCGHLKQCHGQEDGGQTPVMASPCCGCCC GDRSSPPTTPLRAPDPSPGGVPLEASLCPASLAPSGISEKSKSSSSFHPAPGNAQSSSQTPKIVNFVSVGPT YMRVS **(SEQ ID NO: 118)**
IL-18	IL-18Ra	MALPVTALLLPLALLLHAARPYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFII SMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSSY EGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGGGSGGGGSGGGGSGGGGSLQAESCT SRPHITVVEGEPFYLKHCSCSLAHEIETTTKSWYKSSGSQEHVELNPRSSSRIALHDCVLEFWPVELNDT GSYFFQMKNYTQKWKLNVIRRNKHSCFTERQVTSKIVEVKKFFQITCENSYYQTLVNSTSLYKNCKKL LLENNKNPTIKKNAEFEDQGYYSCVHFLHHNGKLFNITKTFNITIVEDRSNIVPVLLGPKLNHVAVELGK NVRLNCSALLNEEDVIYWMFGEENGSDPNIHEEKEMRIMTPEGKWHASKVLRIENIGESNLNVLYNCT VASTGGTDTKSFILVRKADMADIPGHVFTRGMIIAVLILVAVVCLVTVCVIYRVDLVLFYRHLTRRDETLT DGKTYDAFVSYLKECRPENGEEHTFAVEILPRVLEKHFGYKLCIFERDVVPGGAVVDEIHSLIEKSRRLII

		VLSKSYMSNEVRYELESGLHEALVERKIKIILIEFTPVTDFTFLPQSLKLLKSHRVLKWKADKSLSYNSR FWKNLLYLMPAKTVKPGRDEPEVLPVLSES **(SEQ ID NO: 119)**
IL-18	IL-18Rβ	MALPVTALLLPLALLLHAARPYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFII SMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSSY EGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGGGSGGGGSGGGGSGGGGSGGGSLQFNISG CSTKKLLWTYSTRSEEEFVLFCDLPEPQKSHFCHRNRLSPKQVPEHLPFMGSNDLSDVQWYQQPSNGD PLEDIRKSYPHIIQDKCTLHFLTPGVNNSGSYICRPKMIKSPYDVACCVKMILEVKPQTNASCEYSASHK QDLLLGSTGSISCPSLSCQSDAQSPAVTWYKNGKLLSVERSNRIVVDEVYDYHQGTYVCDYTQSDTVS SWTVRAVVQVRTIVGDTKLKPDILDPVEDTLEVELGKPLTISCKARFGFERVFNPVIKWYIKDSDLEWE VSVPEAKSIKSTLKDEIIERNIILEKVTQRDLRRKFVCFVQNSIGNTTQSVQLKEKRGVVLLYILLGTIGT LVAVLAASALLYRHWIEIVLLYRTYQSKDQTLGDKKDFDAFVSYAKWSSFPSEATSSLSEEHLALSLFPD VLENKYGYSLCLLERDVAPGGVYAEDIVSIIKRSRRGIFILSPNYVNGPSIFELQAAVNLALDDQTLKLILI KFCYFQEPESLPHLVKKALRVLPTVTWRGLKSVPPNSRFWAKMRYHMPVKNSQGFTWNQLRITSRIFQ WKGLSRTETTGRSSQPKEW **(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	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgtgcgaccttccacagacccattccctcggctctcgaagaactc tgatgttgctggcccagatgcggaagatttctcttttctcatgtctgaaagacaggcacgactttggttttccccaggaggagttcggaaaccagttccagaaagcgg aaaccattcctgtgctgcacgaaatgatccaacaaattttcaacctgttttcaactaaagatagctccgctgcatgggacgagacactcctcgataagttttatacaga gctttaccagcagttaaatgatctggaagcttgtgtcatccaaggggtcggcgtaaccgagacgcccctgatgaaggaggatagcatactggcagtgcggaagta cttccagaggatcaccctctatctaaaggaaaaaaagtacagtccgtgcgcctgggaagtggttagagccgaaatcatgcgtagcttttccttatctacaaatttgca ggagtcgttgcgcagtaaagagtctggaggcggaagcgggggtggcggcagcggcggtggaggatcaggtggcgggggggtccgggggcggaagtctgca gaagaacctgaaatccccacagaaagtcgaggtggacatcatcgatgacaatttcatcttaagatggaaccgtagcgatgagtccgtcggaaatgtcacattttcttt tgattatcagaagaccgggatggacaactggattaagctgtccggttgccagaacataaccagtaccaagtgtaacttcagcagcctcaaactcaatgtatatgag gaaatcaagctgaggatccgggccgagaaggaaaacacaagctcctggtatgaagttgattcatttactccatttcgaaaagcgcaaataggacccccggaagtt cacctcgaggctgaagataaagcaattgtaatacacatatcgcctggcaccaaggactctgtgatgtgggctttagatgggctgtcattcacgtacagcctggtgat

		ctggaagaacagttctgggtggaggagaagataggaaaacatttatagtcgccacaaaatctacaaattgtcacccgaaacaacctattgcctgaaggtcaaggc
		ggcactattgacgtcctggaagatcggcgtgtactcaccagtgcattgtataaagacacaacagtggaaaacgagcttcccccgccggagaatattgaggtttccgtg
		cagaatcagaattatgttgtgaagtgggactacacatatgccaatatgaccttccaggttcaatggcttcatgcatttctgaaaagaaacccctggtaaccacctttaca
		aatggaagcagattcctgactgcgagaatgtcaagaccacacagtgcgtgtttcctcaaaacgtttccagaaaggcatctatctgctacgggtccaggcttccgat
		ggcaataatacctcatttggagcgaggaaattaaattcgacactgaaatccaagccttcctactcctcccgtatttaacatcaggagtctgtctgatagcttccatatt
		tacatcggtgctcccaagcagtctggaaacactccgtgatccaggattacccctcatctacgagatcatttctgggaaaacacctctaacgccgaacggaagat
		tatagagaagaaaactgacgtcactgtgcctaacctgaaaccattaactgtctattgcgtcaaagctagggcccacaccatggatgaaaaactgaacaagtctagc
		gtgttcagcgacgcagtttgtgagaaaacgaagccaggaaatacttctaagatttggcttatcgtgggcatttgtatcgctctgttcgcactgcccttgtaatctacgc
		cgccaaggttttctccgctgtattaattatgtgttttcccatccctgaagccatcatcgtcgattgacgagtactttctgagcaacctcttaaaaacctgttgttgtcca
		ccagtgaagagcagattgagaaatgcttcattatcgaaaatatttcaacaatcgccacagtggaggagacgaatcagaccgacgaggaccataagaagtacagc
		agtcagacatctcaggattccgggaattacagcaatgaagatgaaagtgaatccaaaactagcgaggagctccaacaggacttttgtg **(SEQ ID NO: 121)**
IFN-α2	IFNAR2	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccgtgcgacctccacagacccattccctcggctctcgaagaactc
		tgatgttgctggcccagatgcggaagatttctctttctcatgtctgaaagacaggcacgacttggtttcccaggaggagttcggaaaccagttccagaaaagcgg
		aaaccattcctgtgctgcacgaaatgatccaacaaatttcaacctgttttcaactaaagatagctccgctgcatgggacgagacactcctcgataagttttatacaga
		gctttaccagcagttaaatgatctggaagcttgtgtcatccaaggggtcggcgtaaccgagacgccccctgatgaaggaggatagcatactggcagtgcggaagta
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Table 11a – Amino Acid Sequences of Exemplary anti-HER2 Chimeric Antigen Receptor (CAR)

CD8a Signal Peptide	MALPVTALLLPLALLLHAARP
HER2 scFv	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGT DFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTGSTSGSGKPGSGEGSEVQLVESGGGLVQP GGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAMDVWGQGTLVTVSSSG **(SEQ ID NO: 159)**
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD **(SEQ ID NO: 160)**

CD8a Transmembrane Domain	IYIWAPLAGTCGVLLLSLVITLYC **(SEQ ID NO: 161)**
CD3ζ Stimulatory Domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR **(SEQ ID NO: 162)**
Complete CAR	MALPVTALLLPLALLLHAARPDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKL LIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTGSTSGSGK PGSGEGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDVWGQGTLVTVSSSGTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCRVKFS RSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR **(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	Gacattcaaatgacacagagtccctcatccctcagtgccagcgtgggcgatcgggtgactataacctgcagagcttctcaggacgtgaataccgctgtggcgtgg taccagcagaagccaggcaaagcgcctaagcttctcatttatagtgccagcttcctgtactcaggtgttccgtctcgcttttctggaagtagaagtgggaccgatttca cattgacgatcagcagcttgcagcccgaagatttcgccacctactactgtcagcagcactacactaccccaccgacatttggtcaaggcacaaaagtagagattaa acgcactggttccaccagcgggagcgggaaacccggctctggggaggggagcgaggtccagctggtggaatccgggggtggtcttgtgcagccaggaggat ccttgaggttgtcctgcgccgcaagcggctttaacatcaaagatacatacatccattgggtccgacaggcccctggaaagggcctggagtgggtcgcccggatct acccaactaacgggtacactcgctacgctgatagcgtcaagggtcggtttactatttctgccgacacctcaaaaaacacagcctacctccagatgaactctctcaga gctgaggatacagccgtgtactattgcagccggtggggaggcgacgggttctacgctatggatgtgtgggggcagggcacactggtcaccgtgagctcatccg ga **(SEQ ID NO: 165)**
CD8a Hinge	Accacgacgccagcgccgcgaccaccaacaccggcgcccaccatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgggggg cgcagtgcacacgaggggggctggacttcgcctgtgat **(SEQ ID NO: 166)**
CD8a Transmembrane Domain	Atctacatctgggcgcccttggccgggacttgtggggtccttctcctgtcactggttatcacccctttactgc **(SEQ ID NO: 167)**

CD3ζ Stimulatory Domain	Agagtgaagttcagcaggagcgcagacgcccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgt tttggacaagagacgtggccgggaccctgagatgggggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatgg cggaggcctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctac gacgcccttcacatgcaggccctgcccccctcgc **(SEQ ID NO: 168)**
Complete CAR	atggccttaccagtgaccgccttgctcctgccgctggccttgctgctccacgccgccaggccggacattcaaatgacacagagtccctcatccctcagtgccagc gtgggcgatcgggtgactataacctgcagagcttctcaggacgtgaataccgctgtggcgtggtaccagcagaagccaggcaaagcgcctaagcttctcatttat agtgccagcttcctgtactcaggtgttccgtctcgcttttctggaagtagaagtgggaccgatttcacattgacgatcagcagcttgcagcccgaagatttcgccacc tactactgtcagcagcactacactaccccaccgacatttggtcaaggcacaaaagtagagattaaacgcactggttccaccagcgggagcgggaaacccggctc tggggaggggagcgaggtccagctggtggaatccgggggtggtcttgtgcagccaggaggatccttgaggttgtcctgcgccgcaagcggctttaacatcaaa gatacatacatccattgggtccgacaggcccctggaaagggcctggagtgggtcgcccggatctacccaactaacgggtacactcgctacgctgatagcgtcaa gggtcggtttactatttctgccgacacctcaaaaaacacagcctacctccagatgaactctctcagagctgaggatacagccgtgtactattgcagccggtgggga ggcgacgggttctacgctatggatgtgtgggggcagggcacactggtcaccgtgagctcatccggaaccacgacgccagcgccgcgaccaccaacaccggc gcccaccatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgggggggcgcagtgcacacgaggggggctggacttcgcctgtgata tctacatctgggcgcccttggccgggacttgtggggtccttctcctgtcactggttatcacccctttactgcagagtgaagttcagcaggagcgcagacgccccgc gtaccagcagggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatggg gggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagc gccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggccctgcccccctcgc **(SEQ ID NO: 169)**

Table 12a – Amino Acid Sequences of Exemplary Co-Stimulatory Ligands

CD40L	MIETYNQTSPRSAATGLPISMKIFMYLLTVFLITQMIGSALFAVYLHRRLDKIEDERNLHEDFVFMKTIQ RCNTGERSLSLLNCEEIKSQFEGFVKDIMLNKEETKKENSFEMQKVLQWAEKGYYTMSNNLVTLENG KQLTVKRQGLYYIYAQVTFCSNREASSQAPFIASLCLKSPGRFERILLRAANTHSSAKPCGQQSIHLGG VFELQPGASVFVNVTDPSQVSHGTGFTSFGLLKL **(SEQ ID NO: 170)**
41BBL	MEYASDASLDPEAPWPPAPRARACRVLPWALVAGLLLLLLLAAACAVFLACPWAVSGARASPGSAA SPRLREGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKELV VAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLPPASSEARNSAFGFQG RLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFRVTPEIPAGLPSPRSE **(SEQ ID NO: 171)**

Table 12b – DNA Sequences of Exemplary Co-Stimulatory Ligands

CD40L	ATGATCGAAACATACAACCAAACTTCTCCCCGATCTGCGGCCACTGGACTGCCCATCAGCATGAA AATTTTTATGTATTTACTTACTGTTTTTCTTATCACCCAGATGATTGGGTCAGCACTTTTTGCTGTGT ATCTTCATAGAAGGTTGGACAAGATAGAAGATGAAAGGAATCTTCATGAAGATTTTGTATTCATG AAAACGATACAGAGATGCAACACAGGAGAAAGATCCTTTATCCTTACTGAACTGTGAGGAGATTA AAAGCCAGTTTGAAGGCTTTGTGAAGGATATAATGTTAAACAAAGAGGAGACGAAGAAAGAAAA CAGCTTTGAAATGCAAAAAAGTGTTACAGTGGGCTGAAAAAGGATACTACACCATGAGCAACAACT TGGTAACCCTGGAAAATGGGAAACAGCTGACCGTTAAAAGACAAGGACTCTATATTATCTATGCC CAAGTCACCTTCTGTTCCAATCGGGAAGCTTCGAGTCAAGCTCCATTTATAGCCAGCCTCTGCCTA AAGTCCCCCGGTAGATTCGAGAGAATCTTACTCAGAGCTGCAAATACCCACAGTTCCGCCAAACC TTGCGGGCAACAATCCATTCACTTGGGAGGAGTATTTGAATTGCAACCAGGTGCTTCGGTGTTTGT CAATGTGACTGATCCAAGCCAAGTGAGCCATGGCACTGGCTTCACGTCCTTTGGCTTACTCAAACT CTGA **(SEQ ID NO: 172)**
41BBL	ATGGAATACGCCTCTGACGCTTCACTGGACCCCGAAGCCCCGTGGCCTCCCGCGCCCCGCTCG CGCCTGCCGCGTACTGCCTTGGGCCCTGGTCGCGGGGCTGCTGCTGCTGCTCGCTGGCCGC CTGCGCCGTCTTCCTCGCCTGCCCCTGGGCCGTGTCCGGGGCTCGCGCCTCGCCCGGCTCCGCGGC CAGCCCGAGACTCCCGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCCGGCCGGCCTCTTGGACCTGC GGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCTGG TACAGTGACCCCAGGCCTGGCAGGCGTGTCCCTGACGGGGGGGCCTGAGCTACAAAGAGGACACGA AGGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGCGTG GTGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCT GGGGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGC CTTCGGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACAC TGAGGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCCGGG TGACCCCCGAAATCCCAGCCGGACTCCCTTCACCGAGGTCGGAATAA **(SEQ ID NO: 173)**

EQUIVALENTS

[0280] 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.

[0281] 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 method of producing a modified immune cell comprising a chimeric antigen receptor (CAR), the method comprising:

administering to a subject a composition comprising:

(a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes the CAR, and

(b) a delivery vehicle;

wherein following administration of the composition one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising the CAR,

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

wherein the modified immune cell comprising the CAR possesses targeted effector activity.

2. A method of treating a disease or disorder in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of the composition comprising:

(a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes a chimeric antigen receptor (CAR), and

(b) a delivery vehicle;

wherein following administration of the composition the one or more nucleic acid molecules are translated in an immune cell to produce a modified immune cell comprising the CAR,

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

wherein at least one sign or symptom of the disease or disorder is improved in the subject after administration.

3. The method of claim 1 or 2, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

4. The method of any one of the preceding claims, wherein the one or more nucleic acid molecules comprise DNA or messenger RNA (mRNA).

5. The method of any one of the preceding claims, wherein the one or more nucleic acid molecules comprise a modification comprising a modified nucleotide, an alteration to the 5' untranslated region (UTR), an alteration to the 3' UTR, a cap structure, a poly(A) tail, or combinations thereof.

6. The method of claim 5, wherein the cap structure comprises AGCap1, m6AGCap1, or Anti-Reverse Cap Analog (ARCA).

7. The method of claim 5 or 6, wherein the modified nucleotide comprises pseudouridine (PsU), 5-methoxyuridine (5moU), 5-methylcytidine/pseudouridine (5meC PsU), N1-methyl-pseudouridine (N1mPsU), or combinations thereof.

8. The method of any one of the preceding claims, wherein the one or more nucleic acid molecules are purified nucleic acid molecules.

9. The method of claim 8, wherein the purified nucleic acid molecules are produced by a method comprising silica membrane purification, high performance liquid chromatography (HPLC), Dynabeads, LiCl precipitation, phenol-chloroform extraction, resin based purification, polyA isolation, RNeasy, or combinations thereof.

10. The method of any one of the preceding claims, wherein one or more nucleic acid molecules are codon-optimized.

11. The method of claim 10, wherein the one or more nucleic acid molecules are codon-optimized for expression in a stem cell, monocyte, macrophage, or dendritic cell.

12. The method of any one of the preceding claims, wherein the composition further comprises an additional payload.

13. The method of claim 12, wherein the additional payload is or comprises a pathogen recognition receptor agonist, polyinosinic:polycytidylic acid (poly I:C), a TLR7/8 agonist, a CpG oligodeoxynucleotide, a NOD-like receptor (NLR) agonist, a RIG-I-like receptor (RLR) agonist, a C-type lectins receptor (CLR) agonist, a cytosolic DNA sensing, the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) agonist, an interferon-inducible protein 16 (IFI16) agonist, a DEAD-box helicase 41 (DDX41) agonist, an LRR binding FLII interacting protein 1 (LRRFIP1) agonist, an absent in melanoma 2 (AIM2) agonist, an aryl hydrocarbon receptor (AhR) ligand, or combinations thereof.

14. The method of claim 12 or 13, wherein one or more nucleic acid molecules and the additional payload are encapsulated within the delivery vehicle.

15. The method of any one of the preceding claims, wherein the delivery vehicle is or comprises a liposome, a lipid nanoparticle, a polymer, an adeno-associated viral (AAV) vector, an adenoviral vector, a retroviral vector or combinations thereof.

16. The method of claim 15, wherein the liposome or lipid nanoparticle comprises one or more cationic lipids, one or more non-cationic lipids, one or more cholesterol-based lipids, one or more PEG-modified lipids, or combinations thereof.

17. The method of claim 15, wherein the retroviral vector comprises a lentiviral vector or a gammaretroviral vector.

18. The method of claim 17, wherein the lentiviral vector is packaged with a Vpx protein.

19. The method of claim 15, wherein the adenoviral vector comprises an Ad2 vector or an Ad5 vector.

20. The method of claim 19, wherein the Ad5 vector comprises an Ad5f35 adenoviral vector.

21. The method of any one of the preceding claims, wherein the step of administering is or comprises transarterial, subcutaneous, intravenous, intradermal, intratumoral, intranodal, intramedullary, intramuscular, or intraperitoneal delivery.

22. The method of any one of the preceding claims, wherein targeted effector activity directed against a target cell is or comprises phagocytosis, targeted cellular cytotoxicity, antigen presentation, or cytokine secretion.

23. The method of any one of the preceding claims, wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent.

24. The method of any one of the preceding claims, wherein at least a portion of the one or more nucleic acid molecules encodes a peptide agent that primes and/or polarizes the modified immune cell toward a pro-inflammatory phenotype.

25. The method of claim 23, wherein the peptide agent is or comprises a cytokine, a cytokine receptor, a chemokine, a chemokine receptor, an immune ligand, a dominant negative receptor, a switch receptor, a secreted antibody or fragment thereof, a transcription factor, an angiopoietin receptor, or combinations thereof.

26. The method of claim 25, wherein following administration of the composition, the one or more nucleic acid molecules are translated in the immune cell to produce the modified immune cell comprising the cytokine, cytokine receptor, chemokine, chemokine receptor, immune ligand,

dominant negative receptor, switch receptor, secreted antibody or fragment thereof, transcription factor, angiopoietin receptor, or combination thereof.

27. The method of claim 23, wherein the portion of the one or more nucleic acid molecules encoding a CAR and the portion of the one or more nucleic acid molecules encoding a peptide agent are present in the composition at a ratio of approximately 1000:1, 500:1, 250:1, 100:1, 50:1, 20:1, 10:1, 5:1, 2:1, 1:1, 1:2, 1:5, 1:10, 1:50, 1:100, 1:250, 1:500, or 1:1000.

28. The method of claim 27, wherein the portion of the one or more nucleic acid molecules encoding a CAR are present in a first delivery vehicle and the portion of the one or more nucleic acid molecules encoding a peptide agent are present in a second delivery vehicle.

29. The method of claim 28, wherein the first delivery vehicle is or comprises a first population of lipid nanoparticles or liposomes and the second delivery vehicle is or comprises a second population of lipid nanoparticles or liposomes.

30. The method of claim 23, wherein the portion of the one or more nucleic acid molecules encoding a CAR and the portion of the one or more nucleic acid molecules encoding a peptide agent are separated by a cleavage peptide.

31. The method of any one of the preceding claims, wherein the composition is administered alone or in combination with one or more therapeutic agents, procedures, or modalities.

32. The method of any one of the preceding claims, wherein the immune cell is mobilized prior to administering the composition to the subject.

33. The method of claim 32, wherein the immune cell is mobilized by administering G-CSF, GM-CSF, FLT3-Ligand, or plerixafor to the subject.

34. A composition comprising:

(a) one or more nucleic acid molecules, wherein at least a portion of the one or more nucleic acid molecules encodes the CAR, and

(b) a delivery vehicle.

35. The composition of claim 34, wherein the delivery vehicle comprises at least one targeting moiety.

36. The composition of claim 35, wherein the targeting moiety facilitates passive targeting of the composition to a desired target.

37. The composition of claim 35, wherein the targeting moiety facilitates active targeting of the composition to a desired target.

38. The composition of claim 37, wherein the targeting moiety is or comprises an antibody or any fragment thereof.

39. The composition of claim 38, wherein the antibody or any fragment thereof binds to CD14, CD11b, CD163, CD206, CD33, CD209, or combinations thereof.

40. The composition of claim 35, wherein the targeting moiety is or comprises a small molecule.

41. The composition of claim 35, wherein the targeting moiety is or comprise a particular lipid or combination of hydrophobic entities.

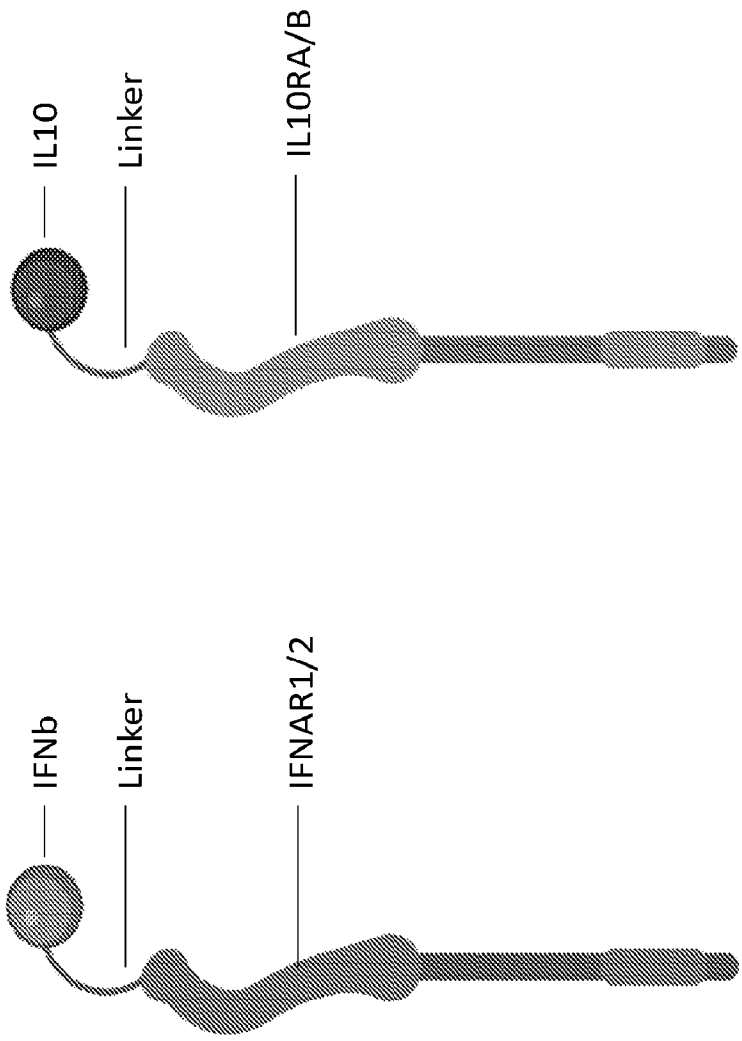

FIGURE 1

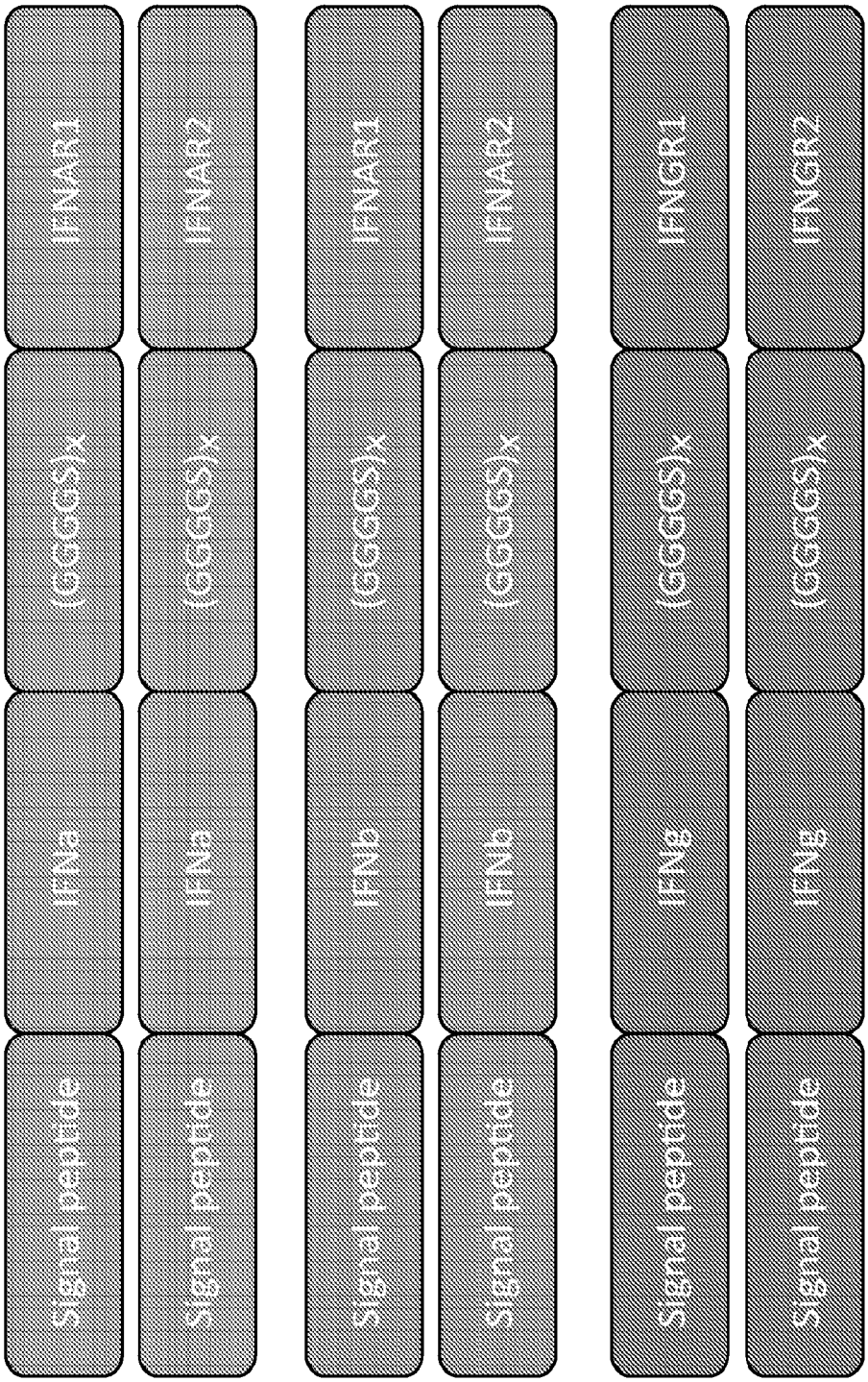
Signal peptide
IFNa
(GGGGS)x
IFNAR1
Signal peptide
IFNa
(GGGGS)x
IFNAR2
Signal peptide
IFNb
(GGGGS)x
IFNAR1
Signal peptide
IFNb
(GGGGS)x
IFNAR2
Signal peptide
IFNe
(GGGGS)x
IFNGR1
Signal peptide
IFNe
(GGGGS)x
IFNGR2

FIGURE 2

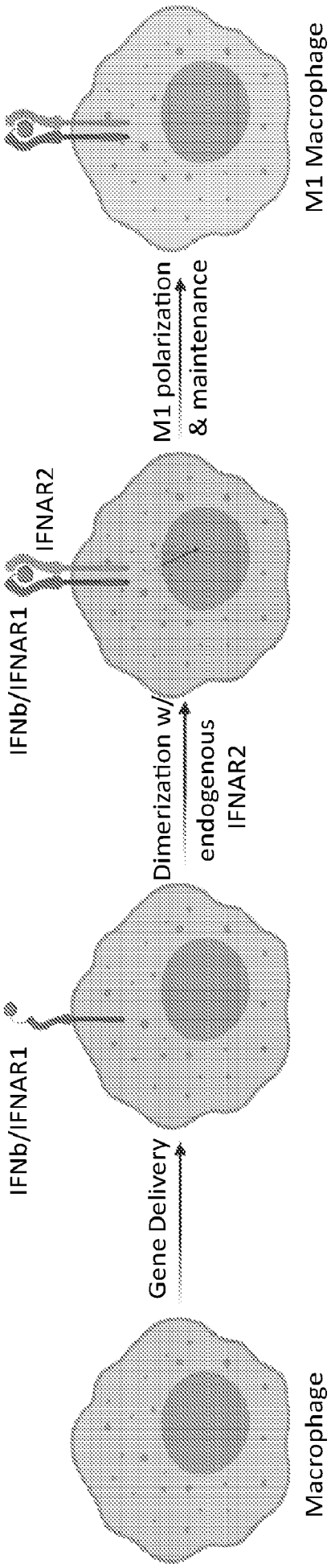
Macrophage
Gene Delivery
IFNb/IFNAR1
Dimerization w/
endogenous
IFNAR2
IFNb/IFNAR1
IFNAR2
M1 polarization
& maintenance
M1 Macrophage

FIGURE 3A

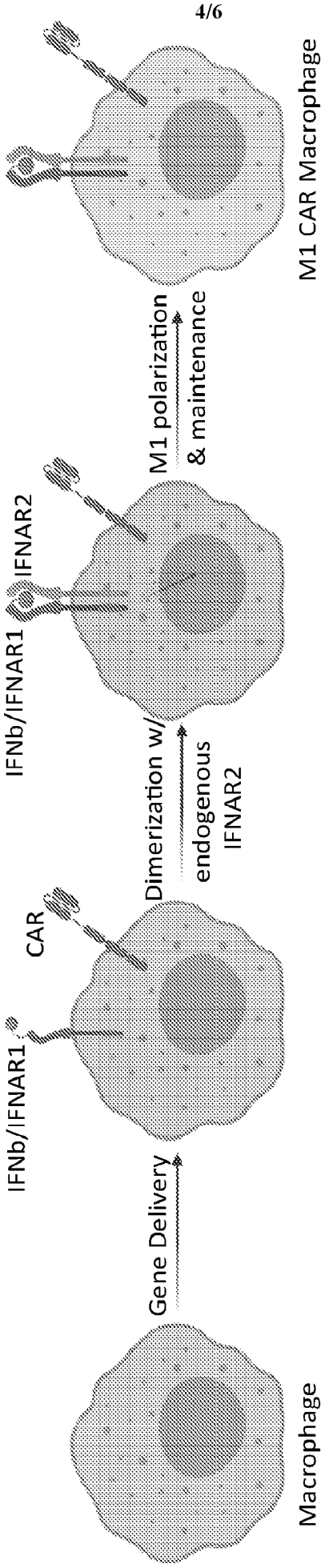
Macrophage
Gene Delivery
IFNb/IFNAR1
CAR
Dimerization w/
endogenous
IFNAR2
IFNb/IFNAR1
IFNAR2
M1 polarization
& maintenance
M1 CAR Macrophage

FIGURE 3B

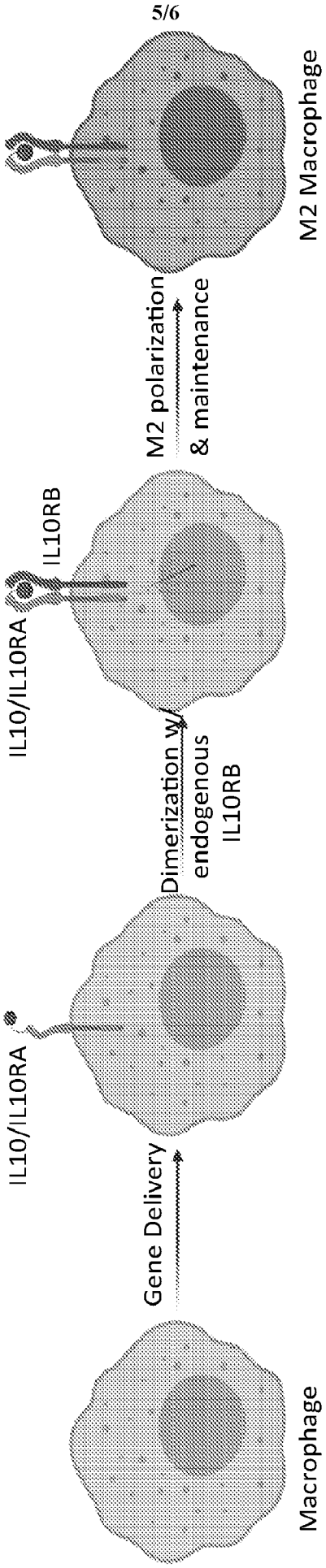
Macrophage
Gene Delivery
IL10/IL10RA
Dimerization w/
endogenous
IL10RB
IL10/IL10RA
IL10RB
M2 polarization
& maintenance
M2 Macrophage

FIGURE 4A

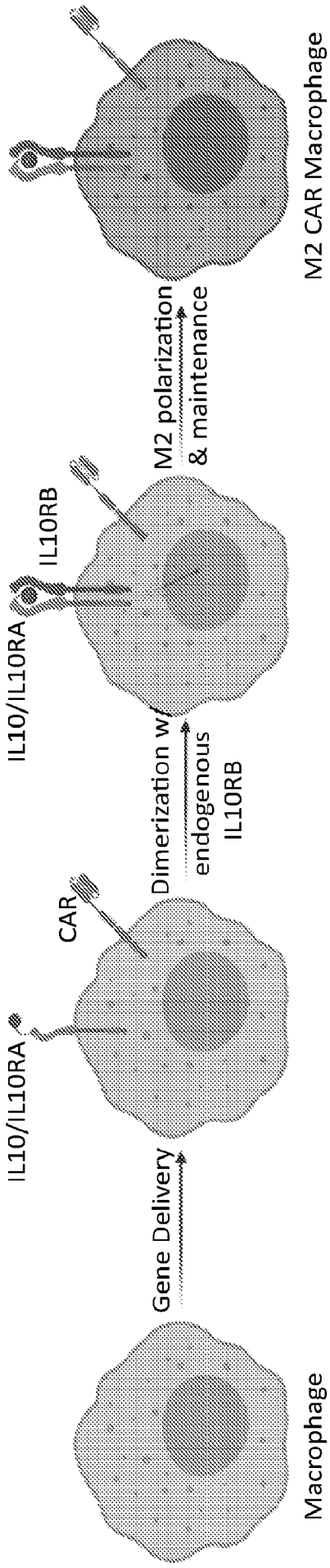
M2 CAR Macrophage
M2 polarization
& maintenance
IL10RB
IL10/IL10RA
Dimerization w/
endogenous
IL10RB
CAR
IL10/IL10RA
Gene Delivery
Macrophage

FIGURE 4B