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(54) **BI-SPECIFIC CHIMERIC ANTIGEN RECEPTORS AND GENETICALLY ENGINEERED IMMUNE CELLS EXPRESSING SUCH**

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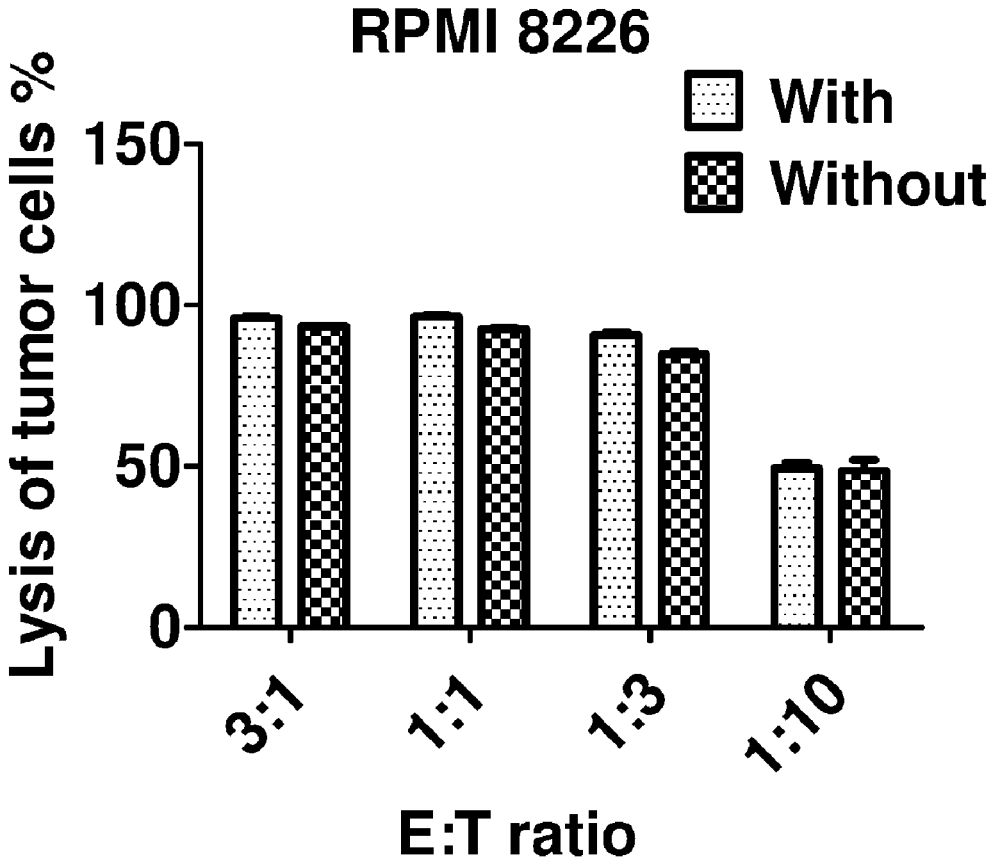
(57) **ABSTRACT**

A bi-specific chimeric antigen receptor (bi-specific CAR) comprising a single chain variable fragment (scFv) and a single variable domain (VHH) in the extracellular antigen binding domain, wherein the scFv and VHH bind tumor associated antigens. Also provided herein are genetically engineered immune cells expressing such bi-specific CAR and therapeutic uses of the genetically engineered immune cells.

Specification includes a Sequence Listing.



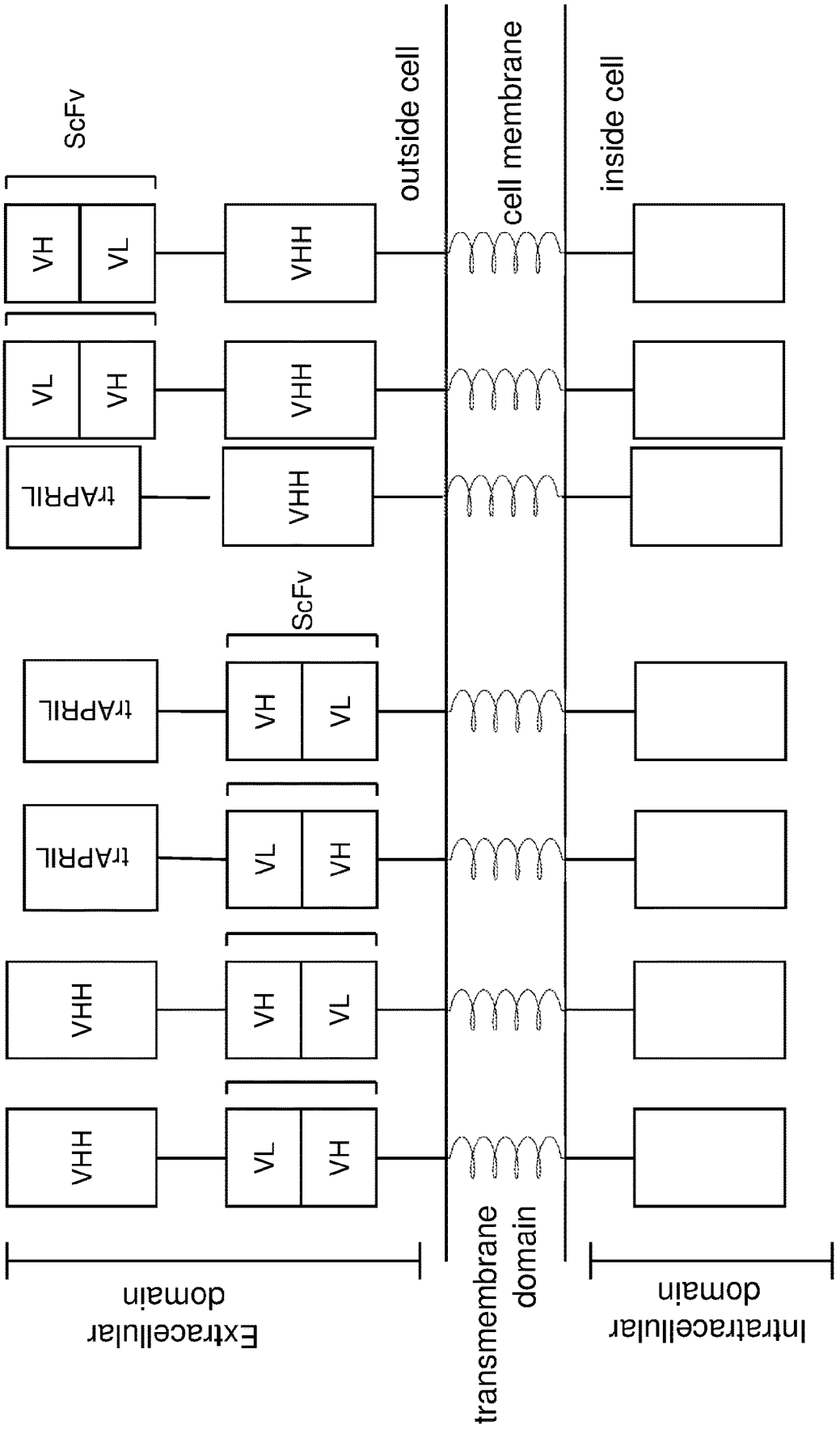

Extracellular domain
transmembrane domain
Intratracellular domain
outside cell
cell membrane
inside cell
ScFv
VH
VL
VHH
trAPRIL

FIG. 1

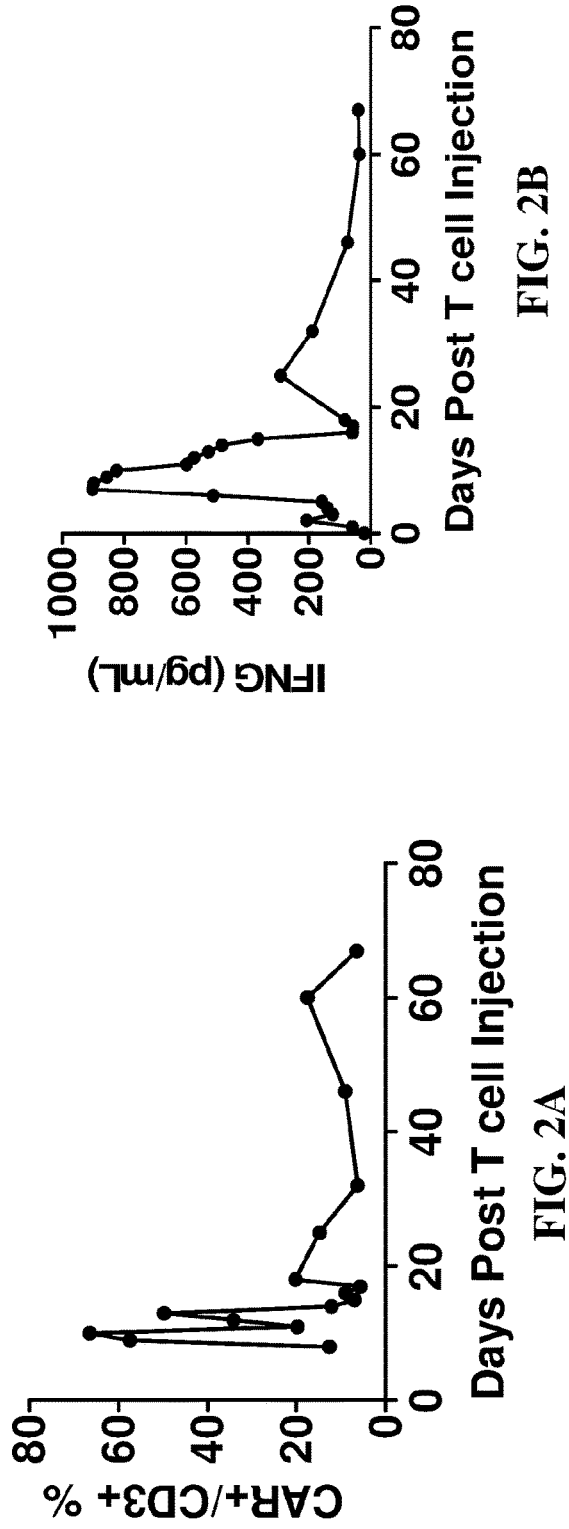


FIG. 2A

FIG. 2B

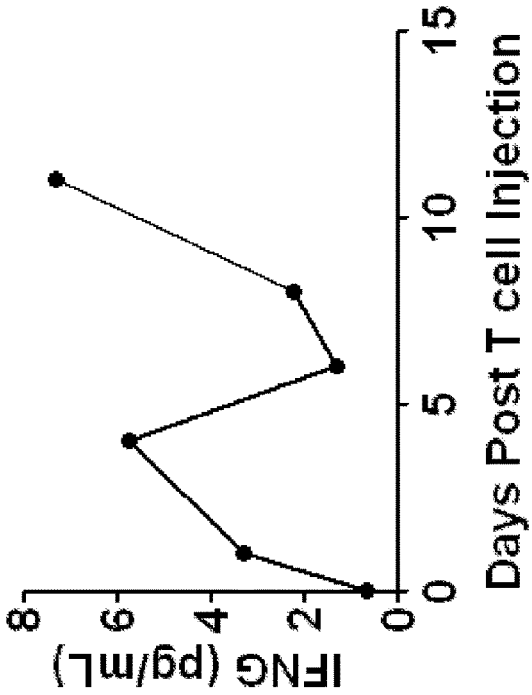


FIG. 2C

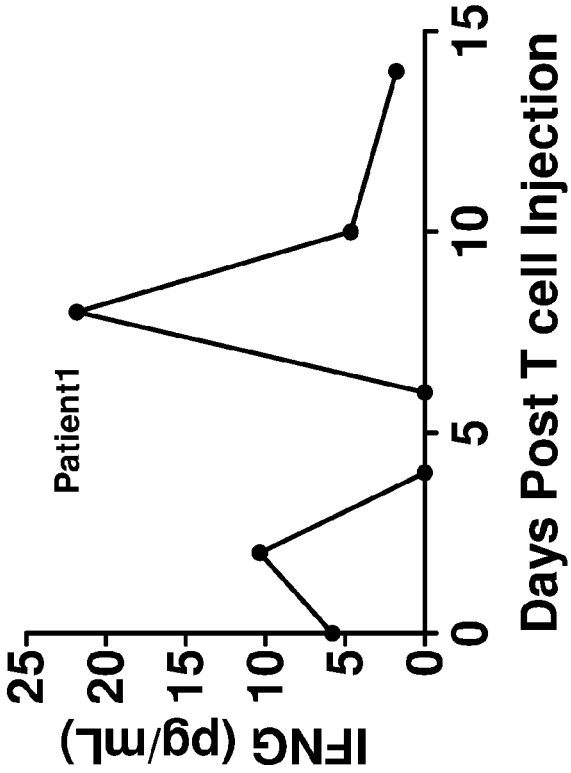

IFNG (pg/mL)
25
20
15
10
5
0
Patient1
0
5
10
15
Days Post T cell Injection

FIG. 3B

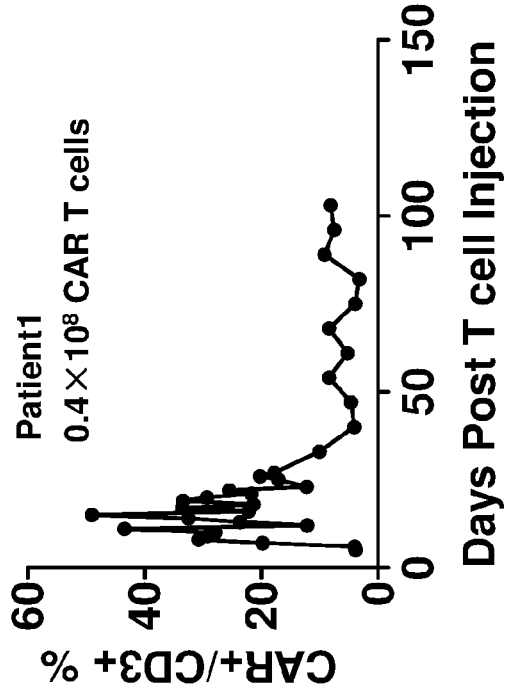

CAR+/CD3+ %
60
40
20
0
Patient1
0.4×10^8 CAR T cells
0
50
100
150
Days Post T cell Injection

FIG. 3A

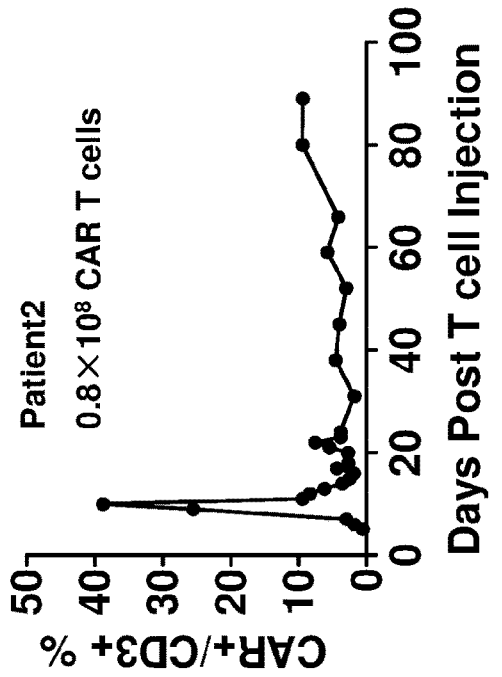


FIG. 3C

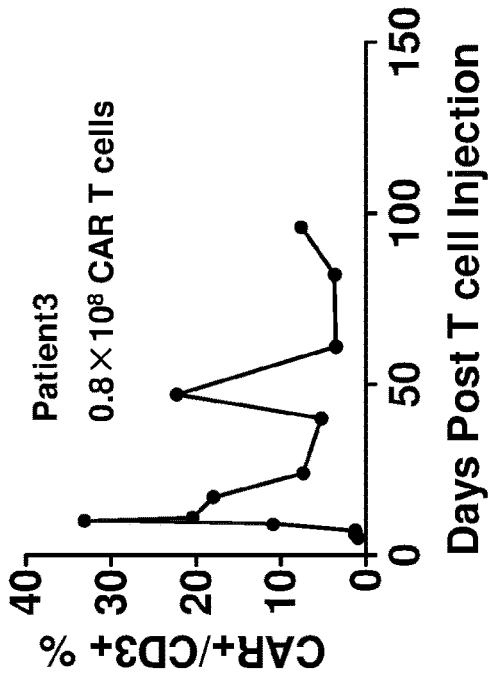


FIG. 3D

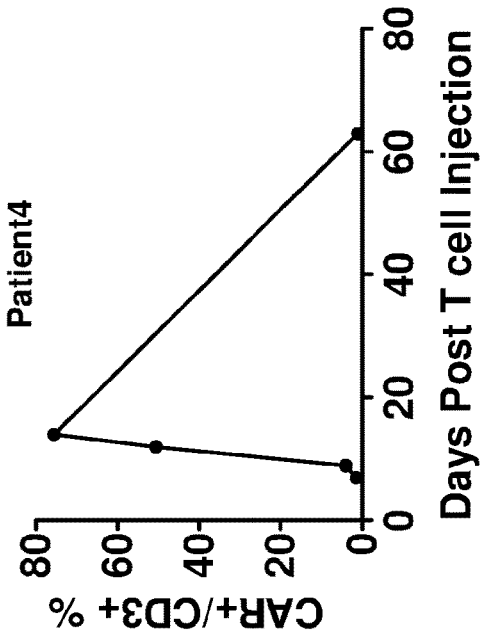


FIG. 3E

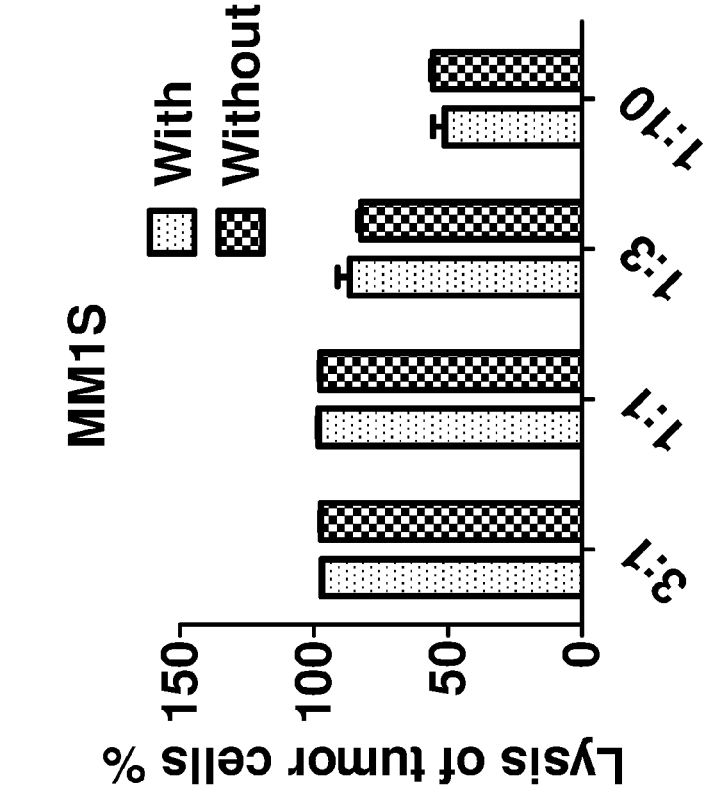

MM1S
With
Without
Lysis of tumor cells %
150
100
50
0
3:1
1:1
1:3
1:10
E:T ratio

FIG. 4B

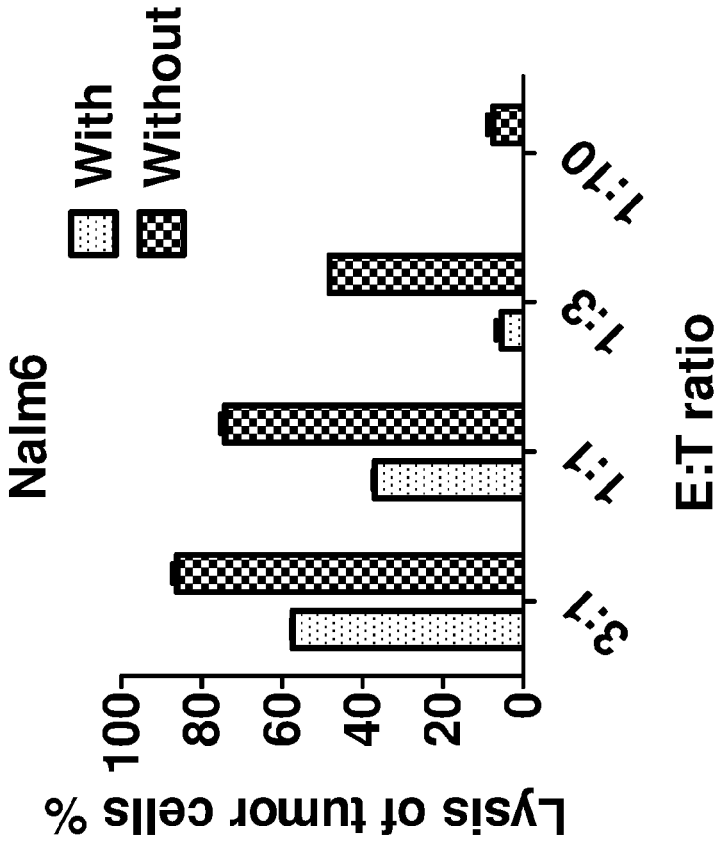

Nalm6
With
Without
Lysis of tumor cells %
100
80
60
40
20
0
3:1
1:1
1:3
1:10
E:T ratio

FIG. 4A


RPMI 8226
With
Without
Lysis of tumor cells %
150
100
50
0
3:1
1:1
1:3
1:10
E:T ratio

FIG. 4C

BI-SPECIFIC CHIMERIC ANTIGEN RECEPTORS AND GENETICALLY ENGINEERED IMMUNE CELLS EXPRESSING SUCH

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/190,480, filed May 19, 2021, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Adoptive cell transfer therapy is a type of immunotherapy that involves ex vivo expansion of autologous or allogeneic immune cells and subsequent infusion into a patient. The immune cells may be modified ex vivo to specifically target malignant cells. Modifications include engineering of T cells to express chimeric antigen receptors (CARs). The promise of adoptive cell transfer therapy, such as CAR T-cell (CAR-T) therapy is often limited by toxicity (e.g., cytokine-associated toxicity). For example, adoptive cell transfer immunotherapy may trigger non-physiologic elevation of cytokine levels (cytokine release syndrome), which could lead to death of recipients (see, e.g., Morgan et al., *Molecular Therapy* 18(4): 843-851, 2010). In addition, modified immune cells may not expand well in patients, may not persist long in vivo, and may be susceptible to the cytotoxic environment initiated by their own activities in vivo.

[0003] It is therefore of great interest to develop approaches to improve the proliferation of these modified immune cells and reduce toxicity associated with CAR-T therapy, while maintaining or enhancing therapeutic efficacy.

SUMMARY OF THE INVENTION

[0004] The present disclosure is based, at least in part, on the development of a bi-specific chimeric antigen receptor (CAR) comprising a bi-specific extracellular antigen binding domain that binds two separate antigens or antigen epitopes, thereby improving therapeutic efficacy of the immune cells expressing such in vivo.

[0005] In some aspects, the present disclosure provides a bi-specific chimeric antigen receptor (CAR) polypeptide, comprising: (a) a first antigen binding moiety, (b) a second antigen binding moiety, (c) a co-stimulatory signaling domain, and (d) a cytoplasmic signaling domain. The first antigen binding moiety can be a single domain antibody variable fragment such as a VHH fragment and the second antigen binding moiety can be a single chain variable fragment (scFv).

[0006] The first antigen binding moiety binds a first tumor-associated antigen, and the second antigen binding moiety binds a second tumor-associated antigen, which is different from the first tumor associated antigen. In some instances, the first and second tumor antigens are selected from 5T4, CD2, CD3, CD5, CD7, CD19, CD20, CD22, CD30, CD33, CD38, CD70, CD123, CD133, CD171, CEA, CS1, BCMA, BAFF-R, PSMA, PSCA, desmoglein (Dsg3), HER-2, FAP, FSHR, NKG2D, GD2, EGFRVIII, mesothelin, ROR1, MAGE, MUC1, MUC16, GPC3, Lewis Y, Claudin 18.2, and VEGFRII. In specific examples, the first tumor antigen is CD19, and the second tumor antigen is BCMA. Alternatively, the first tumor antigen is BCMA, and the second tumor antigen is CD19.

[0007] In some embodiments, the first antigen binding moiety in the bi-specific CAR polypeptide disclosed herein is a VHH fragment binding to CD19 (anti-CD19 VHH) and the second antigen binding moiety is a scFv binding to BCMA (anti-BCMA scFv). Alternatively, the first antigen binding moiety is a VHH binding to BCMA (anti-BCMA VHH) and the second antigen binding moiety is a scFv fragment binding to CD19 (anti-CD19 scFv).

[0008] In some examples, the bi-specific CAR comprises an anti-CD19 scFv, which may comprise the amino acid sequence of SEQ ID. NO: 7, 8, or 9. Alternatively or in addition, the bi-specific CAR further comprises an anti-BCMA VHH, which may comprise the amino acid sequence of SEQ ID NO: 4, 5, or 6. In specific examples, the bi-specific CAR comprises the amino acid sequence of SEQ ID NO: 11 (e.g., as the extracellular bi-specific antigen binding domain).

[0009] In other examples, the bi-specific CAR comprises an anti-CD19 VHH, which may comprise the amino acid sequence of SEQ ID NO: 1, 2, or 3. Alternatively or in addition, the bi-specific CAR further comprises an anti-BCMA scFv, which may comprise the amino acid sequence of SEQ ID NO: 10. Such a bi-specific CAR may comprise the amino acid sequence of SEQ ID NO: 11, 12, 71, or 72. In one specific example, the bi-specific CAR comprises the amino acid sequence of SEQ ID NO: 11 (e.g., as the extracellular bi-specific antigen binding domain). In another specific example, the bi-specific CAR comprises the amino acid sequence of SEQ ID NO: 12 (e.g., as the extracellular bi-specific antigen binding domain).

[0010] In other aspects, the present disclosure provides a bi-specific chimeric antigen receptor (CAR) polypeptide, comprising: (a) a first antigen binding moiety, which is a truncated fragment of APRIL that binds to BCMA; (b) a second antigen binding moiety, which is a single domain antibody variable fragment (VHH) or a single chain variable fragment (scFv) that binds a tumor associated antigen (e.g., CD19), (c) a co-stimulatory signaling domain, and (d) a cytoplasmic signaling domain.

[0011] In some instances, the truncated fragment of APRIL that binds BCMA comprises an amino acid sequence at least 90% identical to SEQ ID NO: 58. In some examples, the truncated fragment of APRIL comprises the amino acid sequence of SEQ ID NO: 58. Alternatively or in addition, the second antigen-binding moiety is an anti-CD19 scFv or an anti-CD19 VHH. In some examples, the second antigen-binding moiety is an anti-CD19 scFv, which may comprise the amino acid sequence of SEQ ID NO: 7, 8, or 9. In other examples, the second antigen-binding moiety is an anti-CD19 VHH, which may comprise the amino acid sequence of SEQ ID NO: 1, 2, or 3. In specific examples, the bi-specific CAR polypeptide may comprise the amino acid sequence of SEQ ID NO: 59, 60, 61, or 62 (e.g., as the extracellular bi-specific antigen binding domain).

[0012] Any of the bi-specific CAR polypeptides disclosed herein may further comprise a peptide linker between the first antigen binding moiety and the second antigen binding moiety. Such a peptide linker may be about 4-40 amino acids in length. In some examples, the bi-specific CAR polypeptide disclosed herein may comprise a co-stimulatory signaling domain from 4-1BB or CD28. Alternatively or in addi-

tion, the cytoplasmic signaling domain in the bi-specific CAR polypeptide may comprise a CD3z cytoplasmic signaling domain, an IL-2RB cytoplasmic signaling domain, or a combination thereof. In specific examples, the cytoplasmic signaling domain in the bi-specific CAR polypeptide comprises both the CD3□ cytoplasmic signaling domain and the IL-2Rβ cytoplasmic signaling domain. In some instances, the cytoplasmic signaling domain comprises the CD3z cytoplasmic signaling domain, which optionally comprises a STAT binding motif, e.g., at the C-terminus.

[0013] Any of the bi-specific CAR polypeptides disclosed herein may further a transmembrane domain, a hinge domain, or a combination thereof. In some instances, the transmembrane domain and/or the hinge domain can be located between the first or second antigen binding moiety and the co-stimulatory domain. In some examples, the transmembrane domain and/or the hinge domain is from CD8.

[0014] Exemplary bi-specific CAR polypeptides provided herein may comprise any of the amino acid sequence of SEQ ID NOs: 63-70.

[0015] In other aspects, the present disclosure also provides a population of genetically engineered immune cells, which expressing a bi-specific CAR polypeptide as disclosed herein. The population of genetically engineered immune cells such as T cells may further comprise one or more of the following features: (a) have one or more disrupted endogenous genes encoding one or more proinflammatory cytokines; and (b) express one or more antagonists targeting the proinflammatory cytokines. In some embodiments, the proinflammatory cytokines include interferon gamma (IFNγ), interleukin 6 (IL-6), GM-CSF, interleukin 1 (IL-1), or a combination thereof.

[0016] In some embodiments, the population of genetically engineered immune cells may comprise a disrupted endogenous interferon gamma gene, a disrupted endogenous GM-CSF gene, or a combination thereof. In some instances, the endogenous interferon gamma gene, the endogenous GM-CSF gene, or both are disrupted by a CRISPR/Cas gene editing system.

[0017] Alternatively or in addition, the genetically engineered immune cells express an IL-6 antagonist, an IFNγ antagonist, an IL-1 antagonist, or a combination thereof. In some examples, the IL-6 antagonist is an antibody specific to human IL6 (anti-IL6 antibody) or an antibody specific to human IL6R (anti-IL6R antibody). In some examples, the IFNγ antagonist is an antibody specific to human IFNγ (anti-IFNγ antibody). In some instances, the anti-IL6 antibody, the anti-IFNγ antibody, or both can be scFv antibodies.

[0018] In some examples, the genetically engineered immune cells express an anti-IFNγ scFv comprising a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 13, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 14. Such an anti-IFNγ scFv may comprise the amino acid sequence of SEQ ID NO: 15. In other examples, the genetically engineered immune cells express an anti-IFNγ scFv comprising a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 16, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 17. Such an anti-IFNγ scFv may comprise the amino acid sequence of SEQ ID NO: 18. In yet other examples, the genetically engineered immune cells express an anti-IFNγ scFv comprising a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 19, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 20. Such an anti-IFNγ scFv may comprise the amino acid sequence of SEQ ID NO: 21.

[0019] In some specific examples, the genetically engineered immune cells expressing any of the anti-IFNγ scFv antibodies disclosed herein may further express a bi-specific CAR comprising the amino acid sequence of SEQ ID NO: 63, 64, 65, or 66.

[0020] In some examples, the genetically engineered immune cells express an anti-IL6 scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 24, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 25. In other examples, the genetically engineered immune cells express an anti-IL6 scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 26, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 27. In yet other examples, the genetically engineered immune cells express an anti-IL6 scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 30, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 31.

[0021] Alternatively, the genetically engineered immune cells express an anti-IL6R scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 22, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 23. In other examples, the genetically engineered immune cells express an anti-IL6R scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 28, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 29. In yet other examples, the genetically engineered immune cells express an anti-IL6R scFv, which may comprise a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 32, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 33.

[0022] In specific examples, the genetically engineered immune cells may express an anti-IL6 scFv or anti-IL6R scFv comprising the amino acid sequence of SEQ ID NO: 34, 35, 36, or 37.

[0023] In some examples, the genetically engineered immune cells express an IL-1 antagonist is IL-1RA, which may comprise the amino acid sequence of SEQ ID NO: 36.

[0024] The population of genetically engineered immune cells disclosed herein may comprise T cells, tumor infiltrating lymphocytes, Natural Killer (NK) cells, dendritic cells, macrographs, B cells, neutrophils, eosinophils, basophils, mast cells, myeloid-derived suppressor cells, mesenchymal stem cells, precursors thereof, or a combination thereof. In some instances, the immune cells are human immune cells. In specific examples, the human immune cells comprise human T cells.

[0025] In addition, the present disclosure provides a pharmaceutical composition, comprising the population of immune cells disclosed herein and a pharmaceutically acceptable carrier.

[0026] In yet other aspects, the present disclosure features a method for reducing or eliminating undesired cells in a

subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the population of immune cells disclosed herein or the pharmaceutical composition comprising such. In some instances, the subject is a human patient having a cancer, which comprises cancer cells expressing the first tumor associated antigen, the second tumor associated antigen, or both.

[0027] In some examples, the subject is a human patient having a solid tumor or a hematological cancer. For example, the human patient may have a solid tumor, which can be breast cancer, lung cancer, pancreatic cancer, liver cancer, glioblastoma (GBM), prostate cancer, ovarian cancer, mesothelioma, colon cancer, or stomach cancer. In other examples, the human patient may have a hematological cancer, which can be leukemia, lymphoma, or multiple myeloma.

[0028] Also within the scope of the present disclosure are immune cell populations and pharmaceutical composition as described herein for use in treating a target disease as described herein (e.g., cancer), and uses of such immune cell population and pharmaceutical composition in manufacturing a medicament for use in treatment of the target disease, such as cancer.

[0029] The details of one or more embodiments of the invention are set forth in the description below. Other features or advantages of the present invention will be apparent from the following drawings and detailed description of several embodiments, and from the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. **1** is a schematic diagram showing exemplary designs of bi-specific chimeric antigen receptor (CAR) polypeptides having tandem arrangements of the antigen binding moieties (e.g., scFv and VHH) in the extracellular antigen-binding domain of the bi-specific CARs.

[0031] FIGS. **2**A-**2**C include diagrams showing CAR-T cell expansion and levels of IFNγ in peripheral blood of ALL patients receiving bi-specific anti-BCMA VHH/anti-CD19 scFv CAR T cells secreting an exemplary anti-IFNγ scFv, and optionally an exemplary anti-IL6 scFv. FIG. **2**A: CAR+ T cell expression from an ALL patient receiving the bi-specific anti-BCMA VHH/anti-CD19 scFv CAR T cells secreting the exemplary anti-IFNγ scFv. FIG. **2**B: peripheral IFNγ level in the ALL patient. FIG. **2**C: levels of IFNγ in peripheral blood of an ALL patient receiving the bi-specific anti-BCMA VHH/anti-CD19 scFv CAR T cells secreting both the exemplary anti-IFNγ scFv and the exemplary anti-IL6 scFv.

[0032] FIGS. **3**A-**3**E include diagrams showing CAR-T cell expansion and levels of IFNγ in peripheral blood of patients diagnosed with refractory and relapsed multiple myeloma (MM) and treated with genetically engineered T cells expressing a bi-specific anti-CD19 VHH scFv/anti-BCMA scFv CAR alone, or in combination with anti-IFNγ scFv. FIGS. **3**A and **3**C-**3**D: CAR-T cell expansion in patients treated with genetically engineered T cells co-expressing the bispecific CAR and the anti-IFNγ scFv. FIG. **3**B: blood levels of IFNγ in an exemplary patient treated with genetically engineered T cells co-expressing the bispecific CAR and the anti-IFNγ scFv. FIG. **3**E: CAR-T cell expansion in a patient treated with genetically engineered T cells expressing the bispecific CAR but not the anti-IFNγ scFv.

[0033] FIGS. **4**A-**4**C include diagrams showing in vitro cytotoxicity of genetically engineered T cells expressing a bi-specific anti-CD19 VHH scFv/anti-BCMA scFv CAR alone, or in combination with anti-IFNγ scFv. FIG. **4**A: targeting Nalm6 cells. FIG. **4**B: targeting MM1S cells. FIG. **4**C: targeting RPMI 8226 cells.

DETAILED DESCRIPTION OF THE INVENTION

[0034] Adoptive cell transfer immunotherapy relies on immune cell activation and cytokine secretion to eliminate disease cells such as cancer cells. However, CAR-T cells do not always expand or activate well in patients.

[0035] The present disclosure aims to overcome limitations associated with current adoptive CAR-T therapy by, e.g., the development of a bi-specific chimeric antigen receptor (CAR) targeting multiple tumor-associated antigens or multiple parts of a tumor associated antigen, thereby improving therapeutic efficacy in vivo. In some instances, the multiple antigen-binding moieties in the bi-specific CAR disclosed herein may be in a combination of single-domain antibody format (e.g., VHH) and single-chain variable fragment (scFv) format.

[0036] It was observed that bi-specific CAR including the scFv-scFv tandem format exhibited CAR expression problems in some instances, which may be caused by the interference between the two scFv binding moieties. Without being bound by theory, the VHH/scFv bi-specific CAR format is designed to solve this potential CAR expression problem. The exemplary bi-specific CARs in the VHH/scFv format tested so far all exhibited satisfactory expression in immune cells. Genetically engineered immune cells (e.g., T cells) expressing the bi-specific CAR disclosed herein may comprise additional genetic modifications, for example, engineered to express an antagonist of a proinflammatory cytokine, engineered to disrupt an endogenous gene of a proinflammatory cytokine, or a combination thereof.

I. Bispecific Chimeric Antigen Receptor

[0037] In some aspects, the present disclosure provides a bi-specific chimeric antigen receptor (CAR) capable of binding to two different tumor-associated antigens or two different antigenic epitopes (which may be in the same antigen) of tumor-associated antigen(s).

[0038] A CAR is an artificial (non-naturally occurring) receptor having binding specificity to a target antigen of interest (e.g., a tumor cell antigen) and capable of triggering immune responses in immune cells expression such upon binding to the target antigen. A CAR often comprises an extracellular antigen-binding domain fused to at least an intracellular signaling domain. Cartellieri et al., *J Biomed Biotechnol* 2010:956304, 2010. The bi-specific CAR disclosed herein comprise two antigen-binding moieties (i.e., a first antigen-binding moiety and a second antigen-binding moiety) having specificity to different target antigens or different antigenic epitopes. In some instances, the bi-specific CAR disclosed herein may be a single polypeptide comprising the two antigen-binding moieties as the extracellular domain and an intracellular domain, which may comprise one or more signaling domains, e.g., a co-stimulatory signaling domain, a cytoplasmic signaling domain, or a combination thereof. The extracellular domain and the

intracellular domain may be linked via a hinge domain, a transmembrane domain, or a combination thereof.

[0039] In some examples, a flexible peptide linker, e.g., a G/S rich linker, may be used to connect two adjacent functional domains, for example, the two antigen-binding moieties. For example, the G/S rich linker may comprise the motif of $(G_4S)_n$, in which n is 1, 2, 3, 4, 5, or 6. Exemplary G/S rich linkers include G_4S (SEQ ID NO: 75), $(G_4S)_3$ (SEQ ID NO: 76), or and $(G_4S)_4$ (SEQ ID NO: 77). In another example, the flexible peptide linker may comprise the motif of EAAAK (SEQ ID NO: 74). Such a peptide linker may contain one or more copies of the motif, e.g., 1, 2, 3, 4, 5, or 6 copies of the motif.

[0040] Exemplary designs of the bi-specific CAR disclosed herein can be found in FIG. **1**.

(a) Bi-Specific Extracellular Antigen Binding Domain

[0041] The extracellular antigen-binding domain of the bi-specific CAR polypeptide disclosed herein is specific to two antigens of interest (e.g., a pathologic antigen such as a tumor-associated antigen, also known as a cancer antigen) or two antigenic epitopes. As used herein, tumor-associated antigens (TAA) are antigens that exhibit elevated levels on tumor cells or a specific type of tumor cells as relative to non-tumor cells or other types of tumor cells.

[0042] The extracellular antigen-binding domain comprises a first antigen-binding domain and a second antigen-binding domain capable of binding to the two antigens of interest (e.g., two tumor-associated antigens) or the two antigenic epitopes of an antigen of interest. Antigens of interest can also be any natural molecules expressed on cells that has been identified as a promising immunotherapy target antigen for various types of cancers.

[0043] In some embodiment, the first antigen-binding domain of the bi-specific CAR polypeptide described herein can be in a single-domain antibody format, for example, a heavy-chain only antibody fragment (VHH), and the second antigen-binding domain can be in a single-chain variable fragment (scFv) format.

[0044] A single-domain antibody such as VHH is a type of antibody containing a single monomeric variable antibody domain. Such antibodies may be derived from the Alpaca heavy chain IgG antibody. Alternatively, VHH antibodies capable of binding to a specific target antigen may be isolated via a conventional method, for example, antibody library screening.

[0045] A scFv fragment contains a heavy chain variable region (VH) and a light chain variable region (VL) linked by a flexible peptide linker. In some examples, the scFv may be in the VH to VL orientation (from N-terminus to C-terminus). Alternatively, the scFv may be in the VL to VL orientation (from N-terminus to C-terminus). The flexible peptide linker for use to connect the VH and VL domains of a scFv fragment (or any two adjacent functional domains in the bi-specific CAR polypeptide disclosed herein) may be a G/S rich peptide linker, which is commonly used in the art in fusion polypeptides. Exemplary peptide linkers are provided in Sequence Table 2 below.

[0046] The VHH and scFv may be connected via a flexible peptide linker such as a G/S peptide linker, which is commonly used in the art for connecting two functional domains. In some instances, the extracellular domain may be in the VHH to scFv orientation (from N-terminus to C-terminus). Alternatively, the extracellular domain may be in the scFv to VHH orientation (from N-terminus to C-terminus). See exemplary arrangements shown in FIG. **1**.

[0047] In some embodiments, the first antigen-binding domain and the second antigen-binding domain may bind to two tumor-associated antigens. Non-limiting examples of tumor associated antigens include 5T4, CD2, CD3, CD5, CD7, CD19, CD20, CD22, CD30, CD33, CD38, CD70, CD123, CD133, CD171, CEA, CS1, BCMA, BAFF-R, seprase (also known as FAP), PSMA, PSCA, desmoglein (Dsg3), HER-2, FAP, FSHR, NKG2D, GD2, EGFRVIII, mesothelin, ROR1, MAGE, MUC1, MUC16, GPC3, Lewis Y, Claudin 18.2, and VEGFRII.

[0048] In other examples, one of the target tumor antigens is FAP, which is a surface-expressed proteolytic enzyme that expressed on cancer-associated fibroblasts (CAFs). FAP is viewed as a major component of the stromal microenvironment of carcinomas such as prostate, lung and pancreatic cancer, and mesothelioma. Moreover, FAP was consistently overexpressed in a large proportion of patient tumors and patient-derived glioblastoma cultures compared to normal tissue.

[0049] In some embodiments, the extracellular antigen-binding domain of the bi-specific CAR targets CD19 and B-cell maturation antigen (BCMA). In some examples, the extracellular antigen-binding domain comprises an anti-CD19 antigen binding domain in VHH format (anti-CD19 VHH). Examples of anti-CD19 VHH fragments are provided in Sequence Table 1 (SEQ ID NOs: 1-3). See, e.g., S. R. Banihashemi, et al., Iran J Basic Med Sci, 21(5):455-464, 2018), and CN 1053848258, the relevant disclosures of which are incorporated by reference for the subject matter and purpose referenced herein. Alternatively, the extracellular antigen-binding domain comprises an anti-CD19 antigen binding domain in scFv format (anti-CD19 scFv). Examples of anti-CD19 scFv are also provided in Sequence Table 1 (SEQ ID NOs: 7-9, 71). See also WO 2020/135335, the content is incorporated herein by reference in its entirety. In some instances, the anti-CD19 VHH or anti-CD19 scFv may be derived from the exemplary anti-CD19 VHH or exemplary anti-CD19 scFv provided in Sequence Table 1, for example, having the same heavy chain and light chain complementary determining regions (CDRs). Heavy and light chain CDRs of the exemplary antibodies listed in Sequence Table 1, determined based on the Kabat definition, are in boldface and underlined.

[0050] The extracellular-binding domain of the bi-specific CAR targeting CD19 and BCMA may comprise an anti-BCMA antigen binding domain in VHH format (anti-BCMA VHH). Examples of anti-BCMA VHH fragments are provided in Sequence Table 1 (SEQ ID NOS: 4-6). See also WO2018/237037, the relevant disclosures of which are incorporated by reference for the subject matter and purpose referenced herein. Alternatively, the extracellular antigen-binding domain comprises an anti-BCMA antigen binding domain in scFv format (anti-BCMA scFv). Examples of anti-BCMA scFv are also provided in Sequence Table 1 (SEQ ID NOs: 10-12, 72). In some instances, the anti-BCMA VHH or anti-BCMA scFv may be derived from any of the exemplary anti-BCMA VHH or exemplary anti-BCMA scFv provided in Sequence Table 1, for example, having the same heavy chain and light chain complementary determining regions (CDRs). Heavy and light chain CDRs

of the exemplary antibodies listed in Sequence Table 1, determined based on the Kabat definition, are in boldface and underlined.

[0051] The anti-CD19/anti-BCMA bi-specific CAR polypeptides described herein may comprise an anti-CD19 VHH binding moiety and an anti-BCMA scFv binding moiety, which may be in any suitable orientation, for example, anti-CD19 VHH/anti-BCMA scFv (N-terminus to C-terminus) or anti-BCMA scFv/anti-CD19 VHH (N-terminus to C-terminus). The anti-CD19 VHH and anti-BCMA scFv fragments may be linked via a flexible peptide linker, e.g., those provided in Sequence Table 1 and Sequence Table 2. Alternatively, the anti-CD19/anti-BCMA bi-specific CAR polypeptides described herein may comprise an anti-BCMA VHH binding moiety and an anti-CD19 scFv binding moiety, which may be in any suitable orientation, for example, anti-BCMA VHH/anti-CD19 scFv (N-terminus to C-terminus) or anti-CD19 scFv/anti-BCMA VHH (N-terminus to C-terminus). The anti-BCMA VHH and anti-CD19 scFv fragments may be linked via a flexible peptide linker, e.g., those provided in Sequence Table 1 and Sequence Table 2.

[0052] In some examples, the anti-CD19/anti-BCMA bi-specific CAR polypeptide described herein comprises (a) an anti-CD19 scFv, which comprises the amino acid sequence of SEQ. ID. NO: 7, 8, or 9, and (b) an anti-BCMA VHH comprising the amino acid sequence of SEQ. ID. NO: 4, 5, or 6.

[0053] In some examples, the anti-CD19/anti-BCMA bi-specific CAR polypeptide described herein comprises (a) an anti-CD19 VHH, which comprises the amino acid sequence of SEQ. ID. NO: 1, 2, or 3, and (b) an anti-BCMA scFv, which comprises the amino acid sequence of SEQ. ID. NO: 10.

[0054] Exemplary extracellular domains of a bi-specific CAR as disclosed herein, which targets both CD19 and BCMA, comprise the amino acid sequence of any one of SEQ ID NOs: 11, 12, 71, and 72 provided in Sequence Table 1.

[0055] In some embodiments, the anti-CD19/anti-BCMA bi-specific CAR polypeptide may comprise (a) a truncated APRIL fragment that binds BCMA (e.g., residues 116 to 250 of the canonical sequence for APRIL (Uniprot 075888), Lee, L. et al., 2018, *Blood,* 131(7): 746-758), and (b) an antigen-binding moiety that binds CD19, e.g., in VHH or scFv format such as any of the anti-CD19 VHH or anti-CD19 scFv disclosed herein (see Sequence Table 1). APRIL (APRoliferation-Inducing Ligand) is a natural high-affinity ligand for BCMA and transmembrane activator and calcium-modulator and cyclophilin ligand (TACI). APRIL is also known as TNFSF13. The amino terminus of APRIL binds proteoglycans but is not involved in the interaction with BCMA or TACI. In some instances, a truncated APRIL fragment (trAPRIL) may comprise (e.g., consisting of) residues 116 to 250 of the naturally-occurring human APRIL for binding to BCMA but having no the proteoglycan binding activity. In one instance, the trAPRIL lacks the N-terminal 115 amino acids from the wild-type APRIL molecule. See U.S. Pat. No. 10,160,794, the relevant disclosures of which are incorporated by reference for the purpose and subject matter referenced herein. As one example, the trAPRIL for making the bi-specific CAR can be set forth as SEQ ID NO:58. Alternatively, the trAPRIL fragment may be at least 85%, 88%, 90%, 92%, 95%, 97%, 99% identity to SEQ ID NO: 58 and binds BCMA. BCMA binding can be determined by any method known in the art, e.g., as described in U.S. Pat. No. 10,160,794.

[0056] In some examples, the anti-CD19 moiety may be an anti-CD19 scFv, e.g., comprising the amino acid sequence of SEQ ID NO: 7, 8, or 9. Alternatively, the anti-CD19 moiety can be an anti-CD19 VHH, e.g., comprising the amino acid sequence of SEQ ID NO: 1, 2, or 3. The anti-CD19 moiety may be linked to the trAPRIL via a flexible peptide linker, e.g., those disclosed herein (e.g., SEQ ID NO: 57 or 73). In some instances, the anti-CD19 moiety can be located at the N-terminal portion relative to the trAPRIL. Alternatively, the trAPRIL can be located at the N-terminal portion relative to the anti-CD19 moiety. Examples of trAPRIL-containing bi-specific extracellular domains include SEQ ID NOs: 59, 60, 61, and 62.

(b) Intracellular Signaling Domains

[0057] Any of the bi-specific CAR polypeptides disclosed herein may further comprise a co-stimulatory domain. Non-limiting sources for co-stimulatory domains include OX40, CD70, CD27, CD28, CD5, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), DAP10, and DAP12. Hence, the CAR may have a co-stimulatory domain derived from 4-1BB, OX40, CD70, CD27, CD28, CD5, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), DAP10, and DAP12 or any combination thereof. In some examples, the bi-specific CAR may comprise a co-stimulatory domain from co-stimulatory receptor 4-1BB (aka CD137), for example, from the human 4-1BB. One exemplary of a 4-1BB co-stimulatory signaling domain comprises (e.g., consists of) the amino acid sequence SEQ ID NO: 39.

[0058] Alternatively or in addition, the bi-specific CAR polypeptide may further comprise a cytoplasmic signaling domain comprising an ITAM such as a CD3ζ signaling domain. Exemplary CD3ζ signaling domains include, but are not limited to, fragments comprising (e.g., consisting of) SEQ ID NO: 43. In some instances, a CD3ζ signaling domain may be modified to insert a STAT binding motif, e.g., linked to its C-terminal portion. The STAT3 binding motif may have the amino acid sequence YX_1X_2Q, where X_1 and X_2 are each independently an amino acid. In particular, the YX_1X_2Q motif may be YRHQ (SEQ. ID. NO: 41). In some examples, the fragment in the CAR construct containing the CD3ζ signaling domain and the STAT3 binding motif may comprise (e.g., consist of) the amino acid sequence of SEQ ID NO: 42.

[0059] In some instances, the bi-specific CAR polypeptide disclosed herein may further comprise an IL-2RB signaling domain, which optionally may be in combination with an ITAM-containing cytoplasmic signaling domain, such as a CD3□ signaling domain, an additional co-stimulatory domain such as that from 4-1BB, or a combination thereof. Without being bound by theory, the presence of the IL2RB signaling domain may significantly improve persistence in vivo of the CAR-T cells expressing the bi-specific CAR polypeptide comprising such. IL2RB is the β chain of the interleukin-2 receptor (IL-2R). An IL-2Rβ signaling domain refers to the fragment in an IL2Rβ polypeptide (e.g., of a suitable species such as human) that is capable of triggering the signaling pathway mediated by the IL-2/IL-2R interaction. IL-2Rβ polypeptides and the signaling domains therein are known in the art. For example, the human IL-2Rβ polypeptide is provided in GENBANK accession number

NP_000869.1 (the contents of which are incorporated herein by reference). IL-2Rβ polypeptides from other species can be obtained from publicly available gene databases such as GENBANK.

[0060] In some examples, the IL2Rβ signaling domain used in the bi-specific CAR polypeptide disclosed herein comprise an amino acid sequence at least 80% (e.g., at least 85%, 90%, 95%, 98% or above) identical to the amino acid sequence of SEQ ID NO: 40. In one example, the IL2Rβ signaling domain comprises (e.g., consists of) SEQ ID NO: 40.

[0061] The "percent identity" of two amino acid sequences is determined using the algorithm of Karlin and Altschul Proc. Natl. Acad. Sci. USA 87:2264-68, 1990, modified as in Karlin and Altschul Proc. Natl. Acad. Sci. USA 90:5873-77, 1993. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. J. Mol. Biol. 215:403-10, 1990. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the protein molecules of interest. Where gaps exist between two sequences, Gapped BLAST can be utilized as described in Altschul et al., Nucleic Acids Res. 25(17):3389-3402, 1997. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

(c) Other CAR Components

[0062] Any of the bi-specific CAR polypeptides disclosed herein may further comprise a transmembrane domain (TMD), a hinge domain, or both. In some examples, the TMD may be located between the extracellular antigen binding domain and the intracellular signaling domain. See FIG. **1**. Alternatively or in addition, the hinge domain may be located between the extracellular antigen-binding domain and the TMD, between the TMD and the intracellular signaling domain, or within the intracellular signaling domain when the intracellular signaling domain comprises a combination of one or more co-stimulatory signaling domain and/or a cytoplasmic signaling domain. Any TMD and/or hinge domains commonly used in bi-specific CAR polypeptide construction can be used here. See U.S. Pat. No. 10,160,794.

[0063] In some examples, the TMD may be obtained from a suitable cell-surface receptor, such as the cell surface receptor of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD3 delta, CD3 gamma, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, CD271, TNFRSF19 and Killer Cell Immunoglobulin-Like Receptor (KIR). In some examples, the hinge domain may be of CD28, CD8, an IgD or an IgG, such as IgG1 or IgG4. See U.S. Pat. No. 10,160,794. In one example, the TMD may be of human CD8a, e.g., comprising or consisting of the amino acid sequence of SEQ. ID. NO:38.

[0064] In some examples, the bi-specific CAR may also comprise a hinge domain, which may be linked to the C-terminus of the bi-specific extracellular antigen binding domain and the N-terminus of the transmembrane domain. Suitable hinge domains can be derived from CD28, CD8, IgD or an IgG; such as IgG1 and IgG4. In one example, the hinge domain may be of human CD8, e.g., comprising or consisting of the amino acid sequence of SEQ. ID. NO:53. In some instances, the TMD and hinge domain may be connected via a flexible peptide linker such as those disclosed herein.

[0065] Any component for use in constructing the bi-specific CAR polypeptides may be a fragment of a naturally-occurring protein (e.g., a cellular receptor such as an immune cell receptor such as those disclosed herein). Alternatively, the CAR component may be a variant of a wild-type counterpart, which may share at least 90% sequence identity to the wild-type counterpart and maintain substantially the same bioactivity. In some instances, the variant may contain up to 15 (e.g., up to 12, 10, 8, 6, 5, 4, 3, 2, or 1) amino acid residue substitutions relative to the wild-type counterpart. In some examples, the one or more amino acid residue substitutions are conservative amino acid residue substitutions.

[0066] As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: ((a) A→G, S; (b) R→K, H; (c) N→Q, H; (d) D→E, N; (e) C→S, A; (f) Q→N; (g) E→D, Q; (h) G→A; (i) H→N, Q; (j) I→L, V; (k) L→I, V; (l) K→R, H; (m) M→L, I, Y; (n) F→Y, M, L; (o) P→A; (p) S→T; (q) T→S; (r) W→Y, F; (s) Y→W, F; and (t) V→I, L.

(d) Exemplary Bi-Specific CAR Polypeptides

[0067] Exemplary bi-specific CAR polypeptides disclosed herein may comprise, from N-terminus to C-terminus, a first antigen-binding moiety, a flexible peptide linker (e.g., SEQ ID NO: 57), a second antigen-binding moiety, a hinge domain (e.g., CD8 hinger such as SEQ ID NO: 53), a transmembrane domain (e.g., a CD8 transmembrane domain such as SEQ ID NO: 38), a co-stimulatory domain (e.g., a 4-1BB co-stimulatory domain such as SEQ ID NO: 39), an IL2Rb signaling domain (e.g., SEQ ID NO: 40), and a cytoplasmic signaling domain (e.g., a CD3z signaling domain such as SEQ ID NO: 42, or 43). In some instances, the bi-specific CAR polypeptide may further comprise a signal peptide at the N-terminus, for example, the exemplary signal peptides provided in Sequence Table 1 (SEQ ID NOs: 45-52)

[0068] In some examples, the bi-specific CAR polypeptide is specific to CD19 and BCMA and comprises the above noted components. Examples include SEQ ID NOs: 64, 66, 68, or 70 (mature polypeptide) and SEQ ID NOs: 63, 65, 67, or 69 (include the N-terminus signal peptide).

II. Genetically Engineered Immune Cells Expressing Bi-Specific CAR

[0069] In one aspect, the present disclosure provides a population of immune cells (e.g., T cells) comprising genetically engineered immune cells (e.g., T cells) that express any

of the bi-specific CAR polypeptides described herein. The population of immune cells may further comprise one or more disrupted endogenous proinflammatory cytokine genes. As used herein, the term "endogenous" refers to naturally originating from within an organism. Alternatively or in addition, the genetically engineered immune cells that express any of the bi-specific CAR polypeptides may further express one or more antagonists (e.g., exogenous) targeting the proinflammatory cytokines. Such genetically engineered immune cells would have inhibited signaling mediated by the proinflammatory cytokine in in vivo. In some instances, the genetically engineered immune cells disclosed herein may exhibit inhibition of more than one cytokine signaling in vivo.

[0070] For purpose of the present disclosure, it will be explicitly understood that the term "antagonist" encompass all the identified terms, titles, and functional states and characteristics whereby the target protein itself, a biological activity of the target protein, or the consequences of the biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree, e.g., by at least 20%, 50%, 70%, 85%, 90%, or above.

[0071] Non-limitation examples of proinflammatory cytokines include IL2, IL1α, IL1β, IL-5, IL-6, IL-7, IL-8, IL-9, IL-12, IL-15, IL-17, IL-18, IL-21, IL-23, sIL-1RI, sIL-2Rα, sIL6R, IFNα, IFNβ, IFNγ, MIPα, MIPβ, CSF1, LIF, G-CSF, GM-CSF, CXCL10, CCL5, eotaxin, TNF, MCP1, MIG, RAGE, CRP, angiopoietin-2, VWF, TGFα, VEGF, EGF, HGF, FGF, perforin, granzyme, and ferritin. In some instances, the proinflammatory cytokines includes interferon gamma (IFNγ), interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 1 (IL-1), or a combination thereof.

A. Immune Cells

[0072] Any immune cells may be used to engineer the cells described herein. In some embodiments, an immune cell can be derived, for example without limitation, from a stem cell. The stem cells can be adult stem cells, non-human embryonic stem cells, more particularly non-human stem cells, cord blood stem cells, progenitor cells, bone marrow stem cells, induced pluripotent stem cells, totipotent stem cells or hematopoietic stem cells. In other embodiments, the immune cell is derived from the differentiation of a population of induced pluripotent cells (iPSCs).

[0073] Useful immune cells for making the engineer the cells disclosed herein may be T-cells, NK cells, tumor infiltrating lymphocytes, dendritic cells, macrophages, B cells, neutrophils, eosinophils, basophils, mast cells, myeloid-derived suppressor cells, mesenchymal stem cells, precursors thereof, or combinations thereof. The T-cells may be selected from the group consisting of inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes. In some embodiments, the T-cells can be derived from the group consisting of CD4+T-lymphocytes and CD8+T-lymphocytes. In one example, the immune cell is a human immune cell. Representative human immune cells are CD34+ cells.

[0074] In some embodiments, the immune cells may be harvested directly from a subject, e.g., a human subject. The cells are genetically modified as described herein and the genetically engineered immune cells are infused back into the same subject, for example, in a CAR-T cell therapy. In this case, the genetically engineered immune cells are autologous to the subject receiving the CAR-T cell therapy. In another embodiment, the immune cells may be harvested directly from a donor subject, modified, and the genetically engineered immune cells are infused into a recipient subject in need of therapy, e.g., a CAR-T cell therapy. The donor immune cells are HLA-matched with to the recipient subject, i.e., the cells are allogeneic to the recipient subject. In some embodiments, the immune cells are harvested from the peripheral blood of the subject, expanded in vitro prior to genetically modification as disclosed herein.

B. Antagonists of Proinflammatory Cytokines

[0075] In some instances, the genetically engineered immune cells disclosed herein may be engineered to express one or more antagonists against proinflammatory cytokines, e.g., those disclosed herein. In some examples, the antagonists are IL-6 antagonistic antibodies, e.g., anti-IL6 antibodies, anti-IL6R antibodies, or anti-gp130 antibodies. Alternatively or in addition, the genetically engineered immune cells may be engineered to express one or more IL-1 antagonists, e.g., IL-1RA or others known in the art or disclosed herein. Alternatively or in addition, the genetically engineered immune cells may be engineered to express one or more IFNγ antagonists, e.g., an antagonistic IFNγ antibody or others known in the art or disclosed herein.

[0076] A typical antibody molecule as disclosed herein comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), which are usually involved in antigen binding. The V_H and V_L regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each V_H and V_L is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the Chothia definition, the AbM definition, and/or the contact definition, all of which are well known in the art. See, e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, Chothia et al., (1989) *Nature* 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also the Human Genome Mapping Project Resources at the Medical Research Council in the United Kingdom and the antibody rules described at the Bioinformatics and Computational Biology group website at University College London.

[0077] An antibody (interchangeably used in plural form) as used herein is an immunoglobulin molecule capable of specific binding to a target protein, e.g., IL-6 or IL-6R, through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses not only intact (e.g., full-length) antibodies and heavy chain antibodies (e.g., an Alpaca heavy chain IgG antibody), but also antigen-binding fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (scFv), single-domain antibody (sdAb; VHH), also known as a nanobody, mutants thereof, fusion proteins comprising an antibody portion, humanized antibodies, chimeric antibodies, diabodies, linear antibodies, single chain

antibodies, multispecific antibodies (e.g., bi-specific antibodies) and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. An antibody includes an antibody of any class, such as IgD, IgE, IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0078] In some embodiments, the antibodies described herein that "bind" a target protein or a receptor thereof may specifically bind to the target protein or receptor. An antibody that "specifically binds" (used interchangeably herein) to a target or an epitope is a term well understood in the art, and methods to determine such specific binding are also well known in the art. A molecule is said to exhibit "specific binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen than it does with alternative targets. An antibody "specifically binds" to a target cytokine if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically (or preferentially) binds to an IL-6 or an IL-6R epitope is an antibody that binds this IL-6 epitope or IL-6R epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other IL-6 epitopes, non-IL-6 epitopes, other IL-6R epitopes or non-IL-6R epitopes. It is also understood by reading this definition that, for example, an antibody that specifically binds to a first target antigen may or may not specifically or preferentially bind to a second target antigen. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

[0079] The antibodies described herein can be murine, rat, human, or any other origin (including chimeric or humanized antibodies). Such antibodies are non-naturally occurring, e.g., would not be produced in an animal without human act (e.g., immunizing such an animal with a desired antigen or fragment thereof).

[0080] Any of the antibodies described herein can be either monoclonal or polyclonal. A "monoclonal antibody" refers to a homogenous antibody population and a "polyclonal antibody" refers to a heterogeneous antibody population. These two terms do not limit the source of an antibody or the manner in which it is made.

[0081] In one example, the antibody used in the methods described herein is a humanized antibody. Humanized antibodies refer to forms of non-human (e.g., murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or antigen-binding fragments thereof that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, and/or six), which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

[0082] In some embodiments, an antagonistic antibody of a target protein as described herein has a suitable binding affinity for the target protein (e.g., human IL-6, human IL-6R, or human IFNγ) or antigenic epitopes thereof. As used herein, "binding affinity" refers to the apparent association constant or KA. The KA is the reciprocal of the dissociation constant (KD). The antagonistic antibody described herein may have a binding affinity (KD) of at least 10-5, 106, 10-7, 10-8, 10-9, 10-10 M, or lower for the target antigen or antigenic epitope. An increased binding affinity corresponds to a decreased KD. Higher affinity binding of an antibody for a first antigen relative to a second antigen can be indicated by a higher KA (or a smaller numerical value KD) for binding the first antigen than the KA (or numerical value KD) for binding the second antigen. In such cases, the antibody has specificity for the first antigen (e.g., a first protein in a first conformation or mimic thereof) relative to the second antigen (e.g., the same first protein in a second conformation or mimic thereof; or a second protein). In some embodiments, the antagonistic antibodies described herein have a higher binding affinity (a higher KA or smaller KD) to the target protein in mature form as compared to the binding affinity to the target protein in precursor form or another protein, e.g., an inflammatory protein in the same family as the target protein. Differences in binding affinity (e.g., for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 105 fold.

[0083] Binding affinity (or binding specificity) can be determined by a variety of methods including equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon resonance, or spectroscopy (e.g., using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH7.4, 150 mM NaCl, 0.005% (v/v) Surfactant P20). These techniques can be used to measure the concentration of bound binding protein as a function of target protein concentration. The

concentration of bound binding protein ([Bound]) is generally related to the concentration of free target protein ([Free]) by the following equation:

$$[Bound]=[Free]/(Kd+[Free])$$

[0084] It is not always necessary to make an exact determination of KA, though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, e.g., determined using a method such as ELISA or FACS analysis, is proportional to KA, and thus can be used for comparisons, such as determining whether a higher affinity is, e.g., 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, e.g., by activity in a functional assay, e.g., an in vitro or in vivo assay.

[0085] Some examples are provided below.

(a) Antagonistic Antibodies Targeting IL6 Signaling

[0086] In some embodiments, the genetically engineered immune cells expressing the bi-specific CAR polypeptide described herein may also express an IL-6 antagonist.

[0087] IL-6 signals through a complex comprising the membrane glycoprotein gp130 and the IL-6 receptor (IL-6R) (see, e.g., Hibi et al., *Cell,* 63(6):1149-57, 1990). IL-6 binding to IL-6R on target cells promotes gp130 homodimerization and subsequent signal transduction. As used herein, IL-6R includes both membrane bound and soluble forms of IL-6R (sIL-6R). When bound to IL-6, soluble IL-6R (sIL-6R) acts as an agonist and can also promote gp130 dimerization and signaling. Trans-signaling can occur whereby sIL-6R secretion by a particular cell type induces cells that only express gp130 to respond to IL-6 (see, e.g., Taga et al., *Annu Rev Immunol.,* 15:797-819, 1997; and Rose-John et al., *Biochem J.,* 300 (Pt 2):281-90, 1994). In one example, sIL-6R comprises the extracellular domain of human IL-6R (see e.g., Peters et al., *J Exp Med.,* 183(4): 1399-406, 1996).

[0088] In some embodiments, the modified immune cells disclosed herein express an IL-6 antagonist, which may be an antibody that binds to IL-6 or to an IL-6 receptor (IL-6R, including gp130). Such antibodies (antagonistic antibodies) can interfere with binding of IL-6/IL-6R on immune cells, thereby suppressing cell signaling mediated by IL-6.

[0089] In some embodiments, the IL-6 antagonistic antibody as described herein can bind and inhibit the IL-6 signaling by at least 50% (e.g., 60%, 70%, 80%, 90%, 95% or greater). The inhibitory activity of an IL-6 antagonistic antibody described herein can be determined by routine methods known in the art.

[0090] The heavy chain variable domains (V_H) and light chain variable domains (V_L) of exemplary anti-IL-6 antibodies and anti-IL-6R antibodies are provided below (Reference Antibodies 1-6) with the CDRs shown in boldface (determined following the antibody rules described by the Bioinformatics and Computational Biology group website at University College London).

[0091] Exemplary antibodies that inhibit the IL-6 signaling pathway, including anti-IL-6 antibodies, anti-IL-6R antibodies, and anti-gp130 antibodies, are provided in Sequence Table 1 (AB1-AB6, and IL6 antagonist scFv1-scFv4), all of which are within the scope of the present disclosure.

[0092] In some embodiments, the IL-6 antagonistic antibodies described herein bind to the same epitope in an IL-6 antigen (e.g., human IL-6) or in an IL-6R (e.g., human IL-6R) as one of the reference antibodies provided herein (e.g., any one of AB1-AB6 such as AB1 or AB2) or compete against the reference antibody from binding to the IL-6 or IL-6R antigen. Reference antibodies provided herein include Antibodies 1-6, the structural features and binding activity of each of which are provided herein. An antibody that binds the same epitope as a reference antibody described herein may bind to exactly the same epitope or a substantially overlapping epitope (e.g., containing less than 3 non-overlapping amino acid residue, less than 2 non-overlapping amino acid residues, or only 1 non-overlapping amino acid residue) as the reference antibody. Whether two antibodies compete against each other from binding to the cognate antigen can be determined by a competition assay, which is well known in the art. Such antibodies can be identified as known to those skilled in the art, e.g., those having substantially similar structural features (e.g., complementary determining regions), and/or those identified by assays known in the art. For example, competition assays can be performed using one of the reference antibodies to determine whether a candidate antibody binds to the same epitope as the reference antibody or competes against its binding to the IL-6 or IL-6R antigen.

[0093] In some instances, the IL-6 antagonistic antibodies disclosed herein may comprise the same heavy chain CDRs and/or the same light chain CDRs as a reference antibody as disclosed herein (e.g., e.g., any one of AB1-AB6 such as AB1 or AB2). The heavy chain and/or light chain CDRs are the regions/residues that are responsible for antigen binding; such regions/residues can be identified from amino acid sequences of the heavy chain/light chain sequences of the reference antibody (shown above) by methods known in the art. See, e.g., antibody rules described at the Bioinformatics and Computational Biology group website at University College London; Almagro, J. Mol. Recognit. 17:132-143 (2004); Chothia et al., J. Mol. Biol. 227:799-817 (1987), as well as others known in the art or disclosed herein. Determination of CDR regions in an antibody is well within the skill of the art, for example, the methods disclosed herein, e.g., the Kabat method (Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda Md.)) or the Chothia method (Chothia et al., 1989, Nature 342:877; Al-lazikani et al (1997) J. Molec. Biol. 273:927-948)). As used herein, a CDR may refer to the CDR defined by any method known in the art. Two antibodies having the same CDR means that the two antibodies have the same amino acid sequence of that CDR as determined by the same method.

[0094] Also within the scope of the present disclosure are functional variants of any of the exemplary anti-IL-6 or anti-IL-6R antibodies as disclosed herein (e.g., any one of AB1-AB6, such as AB1 or AB2). A functional variant may contain one or more amino acid residue variations in the V_H and/or V_L, or in one or more of the HC CDRs and/or one or more of the LC CDRs as relative to the reference antibody, while retaining substantially similar binding and biological activities (e.g., substantially similar binding affinity, binding specificity, inhibitory activity, or a combination thereof) as the reference antibody.

[0095] In some examples, the IL-6 antagonistic antibody disclosed herein comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 10 amino acid variations (e.g., no more than 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1, HC CDR2, and HC CDR3 of a reference antibody

such as any one of AB1-AB6, e.g., AB1 or AB2. "Collectively" means that the total number of amino acid variations in all of the three HC CDRs is within the defined range. Alternatively or in addition, the anti-IL-6 or anti-IL-6R antibody may comprise a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 10 amino acid variations (e.g., no more than 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1, LC CDR2, and LC CDR3 of the reference antibody.

[0096] In some examples, the IL-6 antagonistic antibody disclosed herein may comprise a HC CDR1, a HC CDR2, and a HC CDR3, at least one of which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the counterpart HC CDR of a reference antibody (e.g., any one of AB1-AB6 such as AB1 or AB2). In specific examples, the antibody comprises a HC CDR3, which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the HC CDR3 of a reference antibody (e.g., any one of AB1-AB6 such as AB1 or AB2). Alternatively or in addition, an IL-6 antagonistic antibody may comprise a LC CDR1, a LC CDR2, and a LC CDR3, at least one of which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the counterpart LC CDR of the reference antibody. In specific examples, the antibody comprises a LC CDR3, which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the LC CDR3 of the reference antibody.

[0097] In some instances, the amino acid residue variations can be conservative amino acid residue substitutions. See disclosures herein.

[0098] In some embodiments, the IL-6 antagonistic antibody disclosed herein may comprise heavy chain CDRs that collectively are at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the heavy chain CDRs of a reference antibody such as any one of AB1-AB6, e.g., AB1 or AB2. Alternatively or in addition, the antibody may comprise light chain CDRs that collectively are at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the light chain CDRs of the reference antibody. In some embodiments, the IL-6 antagonistic antibody may comprise a heavy chain variable region that is at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the heavy chain variable region of a reference antibody such as any one of AB1-AB6, e.g., AB1 or AB2; and/or a light chain variable region that is at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the light chain variable region of the reference antibody.

[0099] The present disclosure also provides germlined variants of any of the reference IL-6 antagonistic antibodies disclosed herein. A germlined variant contains one or more mutations in the framework regions as relative to its parent antibody towards the corresponding germline sequence. To make a germlined variant, the heavy or light chain variable region sequence of the parent antibody or a portion thereof (e.g., a framework sequence) can be used as a query against an antibody germline sequence database (e.g., the antibody rules described at the Bioinformatics and Computational Biology group website at University College London; thevbase2 website, or the IMGT®, the international ImMunoGeneTics information system® website) to identify the corresponding germline sequence used by the parent antibody and amino acid residue variations in one or more of the framework regions between the germline sequence and the parent antibody. One or more amino acid substitutions can then be introduced into the parent antibody based on the germline sequence to produce a germlined variant.

[0100] In some examples, the antagonistic antibodies described herein are human antibodies or humanized antibodies. Alternatively or in addition, the antagonistic antibodies are scFv. Exemplary scFv antibodies are provided in Sequence Table 2 below.

(b) IL-1 Antagonists

[0101] In some embodiments, the genetically engineered immune cells expressing the bi-specific CAR described herein may also express an IL-1 antagonist.

[0102] Interleukin-1 is a cytokine known in the art and includes two isoforms, IL-1α and IL-1β. IL-1 plays important roles in up- and down-regulation of acute inflammation, as well as other biological pathways.

[0103] In some examples, the IL-1 antagonist expressed in the genetically engineered immune cells disclosed herein can be an interleukin-1 receptor antagonist (IL-1RA). IL-1RA is a naturally-occurring polypeptide, which can be secreted by various types of cells, such as immune cells, epithelial cells, and adipocytes. It binds to cell surface IL-1R receptor and thereby preventing the cell signaling triggered by IL-1/IL-1R interaction. A human IL-1RA is encoded by the IL1RN gene. In one example, a human IL-1RA comprising the amino acid sequence of SEQ ID NO: 54 (a mature protein). In some instances, the human-IL-1RA may comprise a signal peptide at the N-terminus, e.g., comprising the amino acid sequence of SEQ ID NO: 55 or SEQ ID NO: 56.

[0104] Other IL-1 antagonists include, but are not limited to, anti-IL-1α or anti-IL-1β antibodies (see Fredericks Z L, et al., 2004, *Protein Eng Des Sel.* 17(1):95-106); U.S. Pat. Nos. 7,531,166 and 8,383,778, the contents are incorporated herein by reference in their entireties.

(c) IFNγ Antagonists

[0105] In some embodiments, the genetically engineered immune cell described herein may express an IFNγ antagonist, in combination with the bi-specific CAR disclosed herein, optionally also in combination with one or more additional genetic modifications as also disclosed herein.

[0106] The IFNγ antagonist may block the formation of the ternary IFNγ/IFNγR1/IFNγR2. IFNγ R1 is required for ligand binding and signaling. The IFNγ antagonist can be an antagonistic anti-IFNγ antibody or antigen-binding fragment thereof; a secreted IFNγ receptor or a ligand-binding fragment of the receptor; and an antagonistic anti-IFNγR antibody or antigen-binding fragment thereof, whereby the IFNγ antagonist blocks IFNγ/IFNγR interaction and downstream signaling. In one embodiment, the IFNγ antagonist is secreted. The antagonistic anti-IFNγ antibody or antigen-binding fragment thereof binds the IFNγ ligand that is released in vivo and thus the IFNγ ligand is not available to interact with its native receptor, IFNγR1, expressed on cell surfaces. The secreted IFNγ receptor or a ligand-binding fragment functions as decoy receptor and captures the IFNγ ligand that is released in vivo and thus the IFNγ ligand is also not available to interact with its native receptor, IFNγR1 that is expressed on cell surfaces. In one embodiment, the secreted IFNγR or a ligand-binding fragment is the extracellular portion of a native human IFNγ receptor. The antagonistic anti-IFNγR antibody or antigen-binding frag-

ment thereof binds to the IFNγ receptor expressed on cells and prevents the interaction of the IFNγ ligand with the receptor and the consequential ligand-induced assembly of the complete receptor complex that contains two IFNγR1 and two IFNγR2 subunits. The complete receptor complex is necessary for the IFNγ signaling pathway.

[0107] In some embodiments, the modified immune cells disclosed herein express an IFNγ antagonistic antibody. In some examples, the IFNγ antagonistic antibody as described herein can inhibit the IFNγ signaling by at least 50% (e.g., 60%, 70%, 80%, 90%, 95% or greater). The inhibitory activity of an IFNγ antagonistic antibody described herein can be determined by routine methods known in the art.

[0108] The heavy chain variable domains (V_H) and light chain variable domains (V_L) of exemplary anti-IFNγ antibodies and anti-IL-6R antibodies are provided in Sequence Table 1 below (Reference Anti-IFNγ 1-3) with the CDRs in boldface and underlined (based on the Kabat definition).

[0109] In some embodiments, the IFNγ antagonistic antibodies described herein bind to the same epitope in an IFNγ antigen (e.g., human IFNγ) as one of the reference antibodies provided herein (e.g., any one of Anti-IFNγ 1-3) or compete against the reference antibody from binding to the IFNγ antigen. Reference antibodies provided herein include Anti-IFNγ 1-3, the structural features and binding activity of each of which are provided herein. See Sequence Table 2. In one example, the anti-human IFN-γ antibody may be derived from AMG811, are described in U.S. Pat. No. 7,335,743, the relevant portions of which are incorporated herein by reference for the subject matter and purpose referenced herein. Alternatively, the anti-human IFN-γ antibody may be derived from fontolizumab or emapalumab. Other antagonistic anti-IFNγ antibodies or antigen-binding fragments thereof can be found in U.S. Pat. No. 9,682,142, the content of which is incorporated by reference for the subject matter and purpose referenced herein.

[0110] In some instances, the IFNγ antagonistic antibodies disclosed herein may comprise the same heavy chain CDRs and/or the same light chain CDRs as a reference antibody as disclosed herein (e.g., e.g., any one of Anti-IFNγ 1-3).

[0111] Also within the scope of the present disclosure are functional variants of any of the exemplary anti-IFNγ antibodies as disclosed herein (e.g., any one of Anti-IFNγ 1-3). A functional variant may contain one or more amino acid residue variations in the V_H and/or V_L, or in one or more of the HC CDRs and/or one or more of the LC CDRs as relative to the reference antibody, while retaining substantially similar binding and biological activities (e.g., substantially similar binding affinity, binding specificity, inhibitory activity, or a combination thereof) as the reference antibody.

[0112] In some examples, the IFNγ antagonistic antibody disclosed herein comprises a HC CDR1, a HC CDR2, and a HC CDR3, which collectively contains no more than 10 amino acid variations (e.g., no more than 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the HC CDR1, HC CDR2, and HC CDR3 of a reference antibody such as any one of Anti-IFNγ 1-3. Alternatively or in addition, the anti-IFNγ antibody may comprise a LC CDR1, a LC CDR2, and a LC CDR3, which collectively contains no more than 10 amino acid variations (e.g., no more than 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid variation) as compared with the LC CDR1, LC CDR2, and LC CDR3 of the reference antibody.

[0113] In some examples, the IFNγ antagonistic antibody disclosed herein may comprise a HC CDR1, a HC CDR2, and a HC CDR3, at least one of which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the counterpart HC CDR of a reference antibody (e.g., any one of Anti-IFNγ 1-3). In specific examples, the antibody comprises a HC CDR3, which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the HC CDR3 of a reference antibody (e.g., any one of Anti-IFNγ 1-3). Alternatively or in addition, an IFNγ antagonistic antibody may comprise a LC CDR1, a LC CDR2, and a LC CDR3, at least one of which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the counterpart LC CDR of the reference antibody. In specific examples, the antibody comprises a LC CDR3, which contains no more than 5 amino acid variations (e.g., no more than 4, 3, 2, or 1 amino acid variation) as the LC CDR3 of the reference antibody.

[0114] In some instances, the amino acid residue variations can be conservative amino acid residue substitutions. See disclosures herein.

[0115] In some embodiments, the IFNγ antagonistic antibody disclosed herein may comprise heavy chain CDRs that collectively are at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the heavy chain CDRs of a reference antibody such as any one of Anti-IFNγ 1-3. Alternatively or in addition, the antibody may comprise light chain CDRs that collectively are at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the light chain CDRs of the reference antibody. In some embodiments, the IFNγ antagonistic antibody may comprise a heavy chain variable region that is at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the heavy chain variable region of a reference antibody such as any one of Anti-IFNγ 1-3 and/or a light chain variable region that is at least 80% (e.g., 85%, 90%, 95%, or 98%) identical to the light chain variable region of the reference antibody.

[0116] The present disclosure also provides germlined variants of any of the reference IFNγ antagonistic antibodies disclosed herein. In some examples, the antagonistic antibodies described herein are human antibodies or humanized antibodies. Alternatively or in addition, the antagonistic antibodies are scFv. Exemplary scFv antibodies are provided in Sequence Table 2 below.

[0117] In other embodiments, the INFγ antagonists disclosed herein may be soluble IFNγR fragments, for example, the extracellular portion of a native human IFNγ receptor. Exemplary IFNγR fragments are known in the art, for example, described in U.S. Pat. Nos. 5,578,707 and 7,449,176, the relevant disclosures of each of which are incorporated by reference for the subject matter and purpose referenced herein. The high-affinity IFNγ receptor complex is made up of two type I membrane proteins, IFNγR1 (IFNγR alpha) and IFNγR2 (IFNγR beta). Both proteins are members of the type II cytokine receptor family and share approximately 52% overall sequence identity. IFNγR1 is the ligand-binding subunit that is necessary and sufficient for IFNγ binding and receptor internalization. IFNγR2 is required for IFNγ signaling but does not bind IFNγ by itself. Human IFNγR1 cDNA encodes a 499 amino acid (aa) residue protein with a 17 aa signal peptide, a 228 aa extracellular domain, a 23 aa transmembrane domain, and a

221 aa intracellular domain. Soluble IFNγR fragments that antagonizes the IFNγ signaling may comprises the 228 aa extracellular domain.

[0118] In yet other embodiments, the IFNγ antagonists disclosed herein can be antagonistic anti-IFNγR antibodies or antigen-binding fragments thereof, for example, those described in U.S. Pat. Nos. 4,897,264 and 7,449,176, the relevant disclosures of which are incorporated by reference for the subject matter and purpose referenced herein.

[0119] Any of the IFNγ antagonists described herein may comprising a signal peptide located at the N-terminus of the IFNγ antagonist so that it can be secreted by the genetically engineered immune cells expressing such. Exemplary signal peptides are provided in the Sequence Table 2, any of which can be used in the IFNγ antagonist.

C. Disruption of Endogenous Proinflammatory Cytokine Genes

[0120] In some embodiments, the genetically engineered immune cells expressing any of the bi-specific CARs disclosed herein, optionally also expressing one or more of the antagonists also disclosed herein, may have one or more disrupted endogenous proinflammatory cytokine genes (e.g., the GM-CSF gene and/or the IFNγ gene). Some examples are provided below.

(a) Disruption of Endogenous Interferon Gamma Gene

[0121] In some instances, the genetically engineered immune cells disclosed herein are genetically engineered to provide a reduced level of IFNγ as compared with counterpart immune cells without such a genetic modification, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% lower compared to the counterpart immune cells. The amount of IFNγ produced by such genetically engineered immune cells may be determined by any method know in the art, e.g., by an ELISA assay of the cell culture media or the blood IFNγ level of a patient treated with such modified cells.

[0122] In other instances, the genetically engineered immune cells may reduce a reduced level of IFNγR (e.g., IFNγR1) as compared with the counterpart immune cells that do not have such a genetic modification, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% lower compared to the counterpart immune cells.

[0123] In some examples, reduction of IFNγ may be achieved by disrupting an endogenous IFNγ gene and/or an endogenous IFNγR gene, e.g., by genetic editing. Such genetically engineered immune cells, which express any of the bi-specific CARs disclosed herein, would be expected to have limited cytokine release syndrome mediated by the IFNγ signaling in vivo.

[0124] Any methods known in the art for down-regulating the expression of an endogenous gene in a host cell, including gene editing, can be used to reduce the expression level of IFNγ or IFNγR as described herein. The genomic information for the human IFNγ and IFNγR1 are found in GENBANK Gene ID: 3458 and Gene ID: 3459 respectively.

[0125] In some examples, a gene editing method may be used to disrupt an endogenous IFNγ or IFNγR gene. The gene editing system may involve an endonuclease that is capable of cleaving a target region in the endogenous allele. Non-homologous end joining in the absence of a template nucleic acid may repair double-strand breaks in the genome and introduce mutations (e.g., insertions, deletions and/or frameshifts) into a target site.

[0126] In some examples, a knocking-out event can be coupled with a knocking-in event—an exogenous nucleic acid coding for a desired molecule (e.g., the IL6 antagonist, the IFNγ antagonist or the IL1 antagonist described herein) can be inserted into a genomic locus of the IFNγ or IFNγR gene via gene editing in combination with homologous recombination, to insert the exogenous nucleic acid at the target genomic site, thereby disrupting the endogenous target gene.

[0127] In one example, disrupting an endogenous IFNγ or IFNγR gene can be achieved via a CRISPR/Cas-mediated gene editing method, for example, using a CRISPR/Cas9-mediated gene editing system. To disrupt the IFNγ gene, a guide RNA (gRNA) specific to a target site adjuvant to a protospacer adjacent motif (PAM) may be used. The sgRNAs molecules contains both the custom-designed short crRNA sequence fused to the scaffold tracrRNA sequence. Exemplary genetic target sites in the human IFNγ gene (e.g., in exon 1), the corresponding spacer sequences of gRNAs, and exemplary single guide RNAs (sgRNA) are provided in Sequence Table 3. Any of these gRNAs can be used to disrupt the human IFNγ gene.

[0128] To disrupt the IFNγR gene, commercially available IFNγR1 Human Gene Knockout Kit (CRISPR) Cat #KN202761 from OriGene Technologies may be used. Methods of using such kits are known in the art.

[0129] In other instances, reduction of the level of IFNγ or IFNγR can be achieved by antisense oligonucleotides via the antisense technology or by interfering RNAs (e.g., shRNAs or siRNAs) via the RNA interference technology. Alternatively, ribozymes may be used to achieve this goal. An antisense oligonucleotide or interfering RNA is an oligonucleotide that comprises a fragment complementary to a target region of an endogenous target gene or a transcript thereof. Such antisense oligonucleotides can be delivered into target cells via conventional methods. Alternatively, expression vectors such as lentiviral vectors or equivalent thereof can be used to express such an antisense oligonucleotide or interfering RNA.

D. Populations of Genetically Engineered Immune Cells

[0130] In some aspects, provided herein is a population of genetically engineered immune cells expressing any of the bi-specific CARs described herein (e.g., an anti-CD19/anti-BCMA bi-specific CAR), and comprising one or more additional genetic modifications, e.g., engineered to express one or more antagonists targeting proinflammatory cytokines, engineered to reduce the expression of endogenous proinflammatory cytokines (e.g., via disruption of the endogenous gene by, e.g., gene editing), or a combination thereof.

[0131] In some examples, the genetically engineered immune cells expressing a bi-specific CAR as disclosed herein (e.g., an anti-CD19/anti-BCMA bi-specific CAR) may further express an antagonistic antibody (e.g., an scFv antibody) inhibiting the IL6 signaling, an antagonistic antibody (e.g., an scFv antibody) inhibiting the IFNγ signaling, an IL1 antagonist, or a combination thereof. Examples of such antagonistic agents are disclosed herein.

[0132] Alternatively or in addition, the genetically engineered immune cells disclosed herein may contain one or more disrupted endogenous genes encoding one or more proinflammatory cytokines (e.g., IFNγ or GM-CSF). The genetically engineered immune cells may comprise further genetic editing in genes of interest, for example, the gene encoding a TCR component or the gene encoding a MHC Class I or MHC Class II component. In some instances, a nucleic acid encoding any of the antagonistic agent disclosed herein may be inserted at the disrupted gene locus.

[0133] The population of genetically engineered immune cells may be heterogenous, comprising cells having different genetic modifications or different combination of genetic modifications. For example, a subgroup of cells in the population may co-express the bi-specific CAR and an antagonist of a proinflammatory cytokine and another subgroup of cells in the population may express the bi-specific CAR and have a disrupted endogenous target gene. The cells in the population, collectively, have all of the desired genetic modifications as disclosed herein. In some instances, a portion of the immune cell population may exhibit all of the desired genetic modifications in each cell, e.g., (a) expressing the bi-specific CAR, in combination with expressing an IL6 antagonist and/or an IFNγ antagonist, (b) expressing the bi-specific CAR, in combination with knocking down an endogenous IFNγ gene and/or GM-CSF gene, or (c) expressing the bi-specific CAR, in combination with expressing an IL6 antagonist and/or an IFNγ antagonist and knocking down an endogenous IFNγ gene and/or GM-CSF gene. In some examples, such a portion may constitute at least 20% (e.g., at least 30%, at least 40%, or at least 50%) of the total population of genetically engineered immune cells as disclosed herein.

[0134] Specific knock-in and knock-out genetic modifications for CAR-T cells, including the IFNγ antagonists, IL-6 antagonists and IL-1 antagonists, can be found in WO2019/178259 and WO2020/146239, the relevant disclosures of each of which are incorporated by reference for the purpose and subject matter disclosed herein.

III. Methods of Preparing Genetically Engineered Immune Cells

[0135] Any of the knock-in and knock-out modifications may be introduced into suitable immune cells by routine methods and/or approaches described herein. Typically, such methods would involve delivery of genetic material into the suitable immune cells to either down-regulate expression of a target endogenous inflammatory protein, express a cytokine antagonist of interest or express an immune suppressive cytokine of interest.

(A) Knocking in Modification

[0136] To generate a knock-in of one or more bi-specific CARs, IFNγ antagonists, IL-6 antagonists, and IL-1 antagonists described herein, a coding sequence of the one or more the bi-specific CARs, IFNγ antagonists, IL-6 antagonists, and IL-1 antagonists may be cloned into a suitable expression vector (e.g., including but not limited to lentiviral vectors, retroviral vectors, adenoviral vectors, adeno-associated vectors, PiggyBac transposon vector and Sleeping Beauty transposon vector) and introduced into host immune cells using conventional recombinant technology. Sambrook et al., Molecular Cloning, A Laboratory Manual, 3rd Ed., Cold Spring Harbor Laboratory Press. As a result, modified immune cells of the present disclosure may comprise one or more exogenous nucleic acids encoding at least one bi-specific CAR, IFNγ antagonists, IL-6 antagonist, or IL-1 antagonist. In some instances, the coding sequence of such molecules is integrated into the genome of the cell. In some instances, the coding sequence of such molecules is not integrated into the genome of the cell.

[0137] Knock-in refers to introduce an exogenous nucleic acid into host cells. In some instances, the exogenous nucleic acid may be inserted into a genomic site of the host cells (e.g., for stable expression of the encoded gene product). Alternatively, the exogenous nucleic acid may exist extrachromosomal (e.g., for transient expression of the encoded gene product).

[0138] An exogenous nucleic acid comprising a coding sequence of interest may further comprise a suitable promoter, which can be in operable linkage to the coding sequence. A promoter, as used herein, refers to a nucleotide sequence (site) on a nucleic acid to which RNA polymerase can bind to initiate the transcription of the coding DNA (e.g., for a cytokine antagonist) into mRNA, which will then be translated into the corresponding protein (i.e., expression of a gene). A promoter is considered to be "operably linked" to a coding sequence when it is in a correct functional location and orientation relative to the coding sequence to control ("drive") transcriptional initiation and expression of that coding sequence (to produce the corresponding protein molecules). In some instances, the promoter described herein can be constitutive, which initiates transcription independent other regulatory factors. In some instances, the promoter described herein can be inducible, which is dependent on regulatory factors for transcription. Exemplary promoters include, but are not limited to ubiquitin, RSV, CMV, EF1α and PGK1. In one example, one or more nucleic acids encoding one or more antagonists of one or more inflammatory cytokines as those described herein, operably linked to one or more suitable promoters can be introduced into immune cells via conventional methods to drive expression of one or more antagonists.

[0139] Additionally, the exogenous nucleic acids described herein may further contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; versatile multiple cloning sites; and T7 and SP6 RNA promoters for in vitro transcription of sense and antisense RNA. Suitable methods for producing vectors containing transgenes are well known and available in the art. Sambrook et al., Molecular Cloning, A Laboratory Manual, 3rd Ed., Cold Spring Harbor Laboratory Press.

[0140] In some instances, one or more bi-specific CARs, IFNγ antagonists, IL-6 antagonists, or IL-1 antagonists can be constructed in one expression cassette in a multi-cistronic manner such that the various molecules are expressed as separate polypeptides. In some examples, an internal ribosome entry site can be inserted between two coding sequences to achieve this goal. Alternatively, a nucleotide sequence coding for a self-cleaving peptide (e.g., T2A or

P2A) can be inserted between two coding sequences. Exemplary designs of such multi-cistronic expression cassettes are provided in Examples below.

(B) Knocking Out Modification

[0141] Any methods known in the art for down-regulating the expression of an endogenous gene in a host cell can be used to reduce the production level of a target endogenous cytokine/protein as described herein. A gene editing method may involve use of an endonuclease that is capable of cleaving the target region in the endogenous allele. Non-homologous end joining in the absence of a template nucleic acid may repair double-strand breaks in the genome and introduce mutations (e.g., insertions, deletions and/or frame-shifts) into a target site. Gene editing methods are generally classified based on the type of endonuclease that is involved in generating double stranded breaks in the target nucleic acid. Examples include, but are not limited to, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/endonuclease systems, transcription activator-like effector-based nuclease (TALEN), zinc finger nucleases (ZFN), endonucleases (e.g., ARC homing endonucleases), meganucleases (e.g., mega-TALs), or a combination thereof.

[0142] Various gene editing systems using meganucleases, including modified meganucleases, have been described in the art; see, e.g., the reviews by Steentoft et al., Glycobiology 24(8): 663-80, 2014; Belfort and Bonocora, Methods Mol Biol. 1123:1-26, 2014; Hafez and Hausner, Genome 55(8):553-69, 2012; and references cited therein. In some examples, a knocking-out event can be coupled with a knocking-in event—an exogenous nucleic acid coding for a desired molecule such as those described herein can be inserted into a locus of a target endogenous gene of interest via gene editing.

[0143] Alternatively, any of the knock-out modification may be achieved using antisense oligonucleotides (e.g., interfering RNAs such as shRNA or siRNA) or ribozymes via methods known in the art. An antisense oligonucleotide specific to a target cytokine/protein refers to an oligonucleotide that is complementary or partially complementary to a target region of an endogenous gene of the cytokine or an mRNA encoding such. Such antisense oligonucleotides can be delivered into target cells via conventional methods. Alternatively, expression vectors such as lentiviral vectors or equivalent thereof can be used to express such an antisense oligonucleotides.

(C) Preparation of Immune Cell Population Comprising Modified Immune Cells

[0144] A population of immune cells comprising any of the modified immune cells described herein, or a combination thereof, may be prepared by introducing into a population of host immune cells one or more of the knock-in modifications, one or more of the knock-out modifications, or a combination thereof. The knock-in and knock-out modifications can be introduced into the host cells in any order.

[0145] In some instances, one or more modifications are introduced into the host cells in a sequential manner without isolation and/or enrichment of modified cells after a preceding modification event and prior to the next modification event. In that case, the resultant immune cell population may be heterogeneous, comprising cells harboring different modifications or different combination of modifications. Such an immune cell population may also comprise unmodified immune cells. The level of each modification event occurring in the immune cell population can be controlled by the amount of genetic materials that induce such modification as relative to the total number of the host immune cells. See also above discussions.

[0146] In other instances, modified immune cells may be isolated and enriched after a first modification event before performing a second modification event. This approach would result in the production of a substantially homogenous immune cell population harboring all of the knock-in and/or knock-out modifications introduced into the cells.

[0147] In some examples, the knock-in modification(s) and the knock-out modification(s) are introduced into host immune cells separately. For example, a knock-out modification is performed via gene editing to knock out an endogenous gene for a target cytokine and a knock-in modification is performed by delivering into the host immune cells a separate exogenous expression cassette for producing one or more cytokine antagonists. In some instances, the knock-in and knock-out event can be occurred simultaneously, for example, the knock-in cassette can be inserted into the locus of a target gene to be knocked-out.

IV. Therapeutic Applications

[0148] In some aspects, this disclosure provides a cell therapy-based method of treating a disease or disorder, comprising administering to a subject in need thereof the population of immune cells described herein or a pharmaceutical composition described herein. Any of the immune cell populations comprising the modified immune cells as described herein may be used in an adoptive immune cell therapy (i.e., CAR-T) for treating a target disease, such as leukemia or lymphoma. Due to the knock-in and knock-out modifications introduced into the immune cells, particularly the knock-in of the CAR, the knock-in of the IL-6 antagonistic antibody, the IL-1 antagonist, or a combination thereof, the therapeutic uses of such would be expected to improve proliferation of the therapeutic cells, while achieving the same or better therapeutic effects.

[0149] To practice the therapeutic methods described herein, an effective amount of the immune cell population, comprising any of the modified immune cells as described herein, may be administered to a subject who needs treatment via a suitable route (e.g., intravenous infusion). One or more of the immune cell populations may be mixed with a pharmaceutically acceptable carrier to form a pharmaceutical composition prior to administration, which is also within the scope of the present disclosure. The immune cells may be autologous to the subject, i.e., the immune cells are obtained from the subject in need of the treatment, modified to reduce expression of one or more target cytokines/proteins, for example, those described herein, to express one or more cytokine antagonists described herein, to express a CAR construct and/or exogenous TCR, or a combination thereof. The resultant modified immune cells can then be administered to the same subject. Administration of autologous cells to a subject may result in reduced rejection of the immune cells as compared to administration of non-autologous cells. Alternatively, the immune cells can be allogeneic cells, i.e., the cells are obtained from a first subject, modified as described herein and administered to a second subject that is different from the first subject but of the same species. For

example, allogeneic immune cells may be derived from a human donor and administered to a human recipient who is different from the donor.

[0150] In one embodiment, prior to the cell therapy, the subject received a lymphodepleting treatment to condition the subject for the cell therapy. Examples of lymphodepleting treatment comprises administering to the subject one or more of fludarabine and cyclophosphamide.

[0151] The subject to be treated may be a mammal (e.g., human, mouse, pig, cow, rat, dog, guinea pig, rabbit, hamster, cat, goat, sheep or monkey). The subject may be suffering from cancer, have an infectious disease or an immune disorder. Exemplary cancers include but are not limited to hematologic malignancies (e.g., B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia and multiple myeloma). Exemplary infectious diseases include but are not to human immunodeficiency virus (HIV) infection, Epstein-Barr virus (EBV) infection, human papillomavirus (HPV) infection, dengue virus infection, malaria, sepsis and Escherichia coli infection. Exemplary immune disorders include but are not limited to, autoimmune diseases, such as rheumatoid arthritis, type I diabetes, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, psoriasis, Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, and vasculitis.

[0152] In some instances, the genetically engineered immune cells such as T cells disclosed herein express a bi-specific CAR targeting both CD19 and BCMA (e.g., those disclosed herein). Such bi-specific CAR-T cells can be used to treat human patients having a CD19+ and/or BCMA+ cancer (e.g., a hematological cancer or a solid tumor). In some examples, the cancer may be lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, mantle cell lymphoma, large B-cell lymphoma, or non-Hodgkin's lymphoma. In other examples, the cancer may be multiple myeloma, relapsed multiple myeloma, or refractory multiple myeloma. Alternatively, the human patient may have breast cancer, gastric cancer, neuroblastoma, or osteosarcoma.

[0153] In some embodiments, the CAR-T cells described herein are useful for treating B-cell related cancers. Non-limiting B-cell related cancers include multiple myeloma, malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulienemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmactyic lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma (PBL), large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other B-cell related lymphoma.

[0154] The term "an effective amount" as used herein refers to the amount of each active agent required to confer therapeutic effect on the subject, either alone or in combination with one or more active agents. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, individual patient parameters including age, physical condition, size, gender and weight, the duration of treatment, route of administration, excipient usage, co-usage (if any) with other active agents and like factors within the knowledge and expertise of the health practitioner. The quantity to be administered depends on the subject to be treated, including, for example, the capacity of the individual's immune system to produce a cell-mediated immune response. Precise mounts of active ingredient required to be administered depend on the judgment of the practitioner. However, suitable dosage ranges are readily determinable by one skilled in the art.

[0155] The term "treating" as used herein refers to the application or administration of a composition including one or more active agents to a subject, who has a target disease, a symptom of the target disease, or a predisposition toward the target disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptoms of the disease, or the predisposition toward the disease.

[0156] An effective amount of the immune cells may be administered to a human patient in need of the treatment via a suitable route, e.g., intravenous infusion. In some instances, about 1×10^6 to about 1×10^8 CAR+ T cells may be given to a human patient (e.g., a leukemia patient, a lymphoma patient, or a multiple myeloma patient). In some examples, a human patient may receive multiple doses of the immune cells. For example, the patient may receive two doses of the immune cells on two consecutive days. In some instances, the first dose is the same as the second dose. In other instances, the first dose is lower than the second dose, or vice versa.

[0157] In any of the treatment methods disclosed herein, which involves the use of the immune cells, the subject may be administered IL-2 concurrently with the cell therapy. More specifically, an effective amount of IL-2 may be given to the subject via a suitable route before, during, or after the cell therapy. In some embodiments, IL-2 is given to the subject after administration of the immune cells.

[0158] Alternatively or in addition, the subject being treated by the cell therapy disclosed herein may be free from treatment involving an IL-6 antagonist (aside from an IL-6 antagonist produced by the immune cells used in the cell therapy) after immune cell infusion.

[0159] The immune cell populations comprising the modified immune cells as described herein may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth. Such therapies can be administered simultaneously or sequentially (in any order) with the immunotherapy described herein. When co-administered with an additional therapeutic agent, suitable therapeutically effective dosages for each agent may be lowered due to the additive action or synergy.

[0160] In some embodiments, the method of treating cancer does not elicit severe CRS in the subject being treated within 14 days of infusion of the genetically engineered cells. In one embodiment of the treatment methods, the subject being treated may not need to receive additional anti-IL-6 therapy such as tocilizumab. In some embodiments, the subject being treated may not need to receive steroid therapy to suppress the immune system. In other embodiments, the subject being treated may receive immunosuppressive steroids such as methylprednisolone and dexamethasone in conjunction with infusion of the immune cells disclosed herein. A skilled clinician will be able to determine the vital signs and symptoms of the subject to monitor and assess for the grade/severity of CRS during treatment and timely administer appropriate medication to suppress the developing CRS.

[0161] In some examples, the subject is subject to a suitable anti-cancer therapy (e.g., those disclosed herein) to reduce tumor burden prior to the CAR-T therapy disclosed herein. For example, the subject (e.g., a human cancer patient) may be subject to a chemotherapy (e.g., comprising a single chemotherapeutic agent or a combination of two or more chemotherapeutic agents) at a dose that substantially reduces tumor burden. In some instances, the chemotherapy may reduce the total white blood cell count in the subject to lower than 10^8/L, e.g., lower than 10^7/L. Tumor burden of a patient after the initial anti-cancer therapy, and/or after the CAR-T cell therapy disclosed herein may be monitored via routine methods. If a patient showed a high growth rate of cancer cells after the initial anti-cancer therapy and/or after the CAR-T therapy, the patient may be subject to a new round of chemotherapy to reduce tumor burden followed by any of the CAR-T therapy as disclosed herein.

[0162] Non-limiting examples of other anti-cancer therapeutic agents useful for combination with the modified immune cells described herein include, but are not limited to, immune checkpoint inhibitors (e.g., PDL1, PD1, and CTLA4 inhibitors), anti-angiogenic agents (e.g., TNP-470, platelet factor 4, thrombospondin-1, tissue inhibitors of metalloproteases, prolactin, angiostatin, endostatin, bFGF soluble receptor, transforming growth factor beta, interferon alpha, interferon gamma, soluble KDR and FLT-1 receptors, and placental proliferin-related protein); a VEGF antagonist (e.g., anti-VEGF antibodies, VEGF variants, soluble VEGF receptor fragments); chemotherapeutic compounds. Exemplary chemotherapeutic compounds include pyrimidine analogs (e.g., 5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine); purine analogs (e.g., fludarabine); folate antagonists (e.g., mercaptopurine and thioguanine); antiproliferative or antimitotic agents, for example, *vinca* alkaloids; microtubule disruptors such as taxane (e.g., paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, and epidipodophyllotoxins; DNA damaging agents (e.g., actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, hexamethyhnelamineoxaliplatin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, plicamycin, procarbazine, taxol, taxotere, teniposide, triethylenethiophosphoramide and etoposide).

[0163] In some embodiments, radiation or radiation and chemotherapy is used in combination with the cell populations comprising modified immune cells described herein. Additional useful agents and therapies can be found in Physician's Desk Reference, 59.sup.th edition, (2005), Thomson P D R, Montvale N.J.; Gennaro et al., Eds. Remington's The Science and Practice of Pharmacy 20.sup.th edition, (2000), Lippincott Williams and Wilkins, Baltimore Md.; Braunwald et al., Eds. Harrison's Principles of Internal Medicine, 15.sup.th edition, (2001), McGraw Hill, NY; Berkow et al., Eds. The Merck Manual of

Diagnosis and Therapy, (1992), Merck Research Laboratories, Rahway N.J.

V. Kits for Therapeutic Uses or Making Genetically Engineered Immune Cells

[0164] The present disclosure also provides kits for use of any of the target diseases described herein involving one or more of the immune cell population described herein and kits for use in making the modified immune cells as described herein.

[0165] A kit for therapeutic use as described herein may include one or more containers comprising an immune cell population, which may be formulated to form a pharmaceutical composition. The immune cell population comprises any of the modified immune cells described herein or a combination thereof. The population of immune cells, such as T lymphocytes, NK cells, and others described herein may further express a bi-specific CAR construct as described herein.

[0166] In some embodiments, the kit can additionally comprise instructions for use of the immune cell population in any of the methods described herein. The included instructions may comprise a description of administration of the immune cell population or a pharmaceutical composition comprising such to a subject to achieve the intended activity in a subject. The kit may further comprise a description of selecting a subject suitable for treatment based on identifying whether the subject is in need of the treatment. In some embodiments, the instructions comprise a description of administering the immune cell population or the pharmaceutical composition comprising such to a subject who is in need of the treatment.

[0167] The instructions relating to the use of the immune cell population or the pharmaceutical composition comprising such as described herein generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the disclosure are typically written instructions on a label or package insert. The label or package insert indicates that the pharmaceutical compositions are used for treating, delaying the onset, and/or alleviating a disease or disorder in a subject.

[0168] The kits provided herein are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging, and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device, or an infusion device. A kit may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port. At least one active agent in the pharmaceutical composition is a population of immune cells (e.g., T lymphocytes or NK cells) that comprise any of the modified immune cells or a combination thereof.

[0169] Kits optionally may provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container. In some embodiment, the disclosure provides articles of manufacture comprising contents of the kits described above.

[0170] Also provided here are kits for use in making the modified immune cells as described herein. Such a kit may include one or more containers each containing reagents for use in introducing the knock-in and/or knock-out modifications into immune cells. For example, the kit may contain one or more components of a gene editing system for making one or more knock-out modifications as those described herein. Alternatively or in addition, the kit may comprise one or more exogenous nucleic acids for expressing cytokine antagonists as also described herein and reagents for delivering the exogenous nucleic acids into host immune cells. Such a kit may further include instructions for making the desired modifications to host immune cells.

General Techniques

[0171] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, immunology and chimeric antigen receptor (CAR) immunotherapy, which are within the skill of the art. Such techniques are explained fully in the literature, such as *Molecular Cloning: A Laboratory Manual*, second edition (Sambrook, et al., 1989) Cold Spring Harbor Press; *Oligonucleotide Synthesis* (M. J. Gait, ed. 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J. E. Cellis, ed., 1989) Academic Press; *Animal Cell Culture* (R. I. Freshney, ed. 1987); *Introduction to Cell and Tissue Culture* (J. P. Mather and P. E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J. B. Griffiths, and D. G. Newell, eds. 1993-8) J. Wiley and Sons; *Methods in Enzymology* (Academic Press, Inc.); *Handbook of Experimental Immunology* (D. M. Weir and C. C. Blackwell, eds.): *Gene Transfer Vectors for Mammalian Cells* (J. M. Miller and M. P. Calos, eds., 1987); *Current Protocols in Molecular Biology* (F. M. Ausubel, et al. eds. 1987); *PCR: The Polymerase Chain Reaction*, (Mullis, et al., eds. 1994); *Current Protocols in Immunology* (J. E. Coligan et al., eds., 1991); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); Immunobiology (C. A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); *Antibodies: a practice approach* (D. Catty., ed., IRL Press, 1988-1989); *Monoclonal antibodies: a practical approach* (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); *Using antibodies: a laboratory manual* (E. Harlow and D. Lane, Cold Spring Harbor Laboratory Press, 1999); *The Antibodies* (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); *DNA Cloning: A practical Approach*, Volumes I and II (D. N. Glover ed. 1985); *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1985); *Transcription and Translation* (B. D. Hames and S. J. Higgins, eds. 1984); *Animal Cell Culture* (R. I. Freshney, ed., 1986); *Immobilized Cells and Enzymes* ((B. Perbal, IRL Press, 1986); *A practical Guide To Molecular Cloning* (F. M. Ausubel et al., eds 1984); *Chimeric Antigen Receptor (CAR) Immunotherapy* (D. W. Lee and N. N. Shah, eds., Elservier, 2019, ISBN: 9780323661812); *Basics of Chimeric Antigen Receptor* (CAR) *Immunotherapy* (M. Y. Balkbi, Academic Press, Elsevier Science, 2019, ISBN: 9780128197479); *Chimeric Antigen Receptor T Cells Development and Production* (V. Picanço-Castro, K. C. R. Malmegrim, K. Swiech, eds., Springer US, 2020, ISBN: 9781071601488); *Cell and Gene Therapies* (C. Bollard, S. A. Abutalib, M.-A. Perales eds., Springer International, 2018; ISBN: 9783319543680) and *Developing Costimulatory Molecules for Immunotherapy of Diseases* (M. A. Mir, Elsevier Science, 2015, ISBN: 9780128026755).

[0172] The present disclosure is not limited in its application to the details of construction and the arrangements of component set forth in the description herein or illustrated in the drawings. The present disclosure is capable of other embodiments and of being practice or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items. As also used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise.

[0173] Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference for the purposes or subject matter referenced herein.

SEQUENCE TABLE 1

Antibody Sequences.

Description	Sequence (CDRs in boldface and underlined; determined by the Kabat method)	SEQ ID NO
Anti-CD19 VHH 1	EVQLLESGGGLVQPGGSLRSCEASGF**NAMT**WVRQPPGKG LEWVS**SIDSWTDAVKG**RFAISQDNAKNTVYLQMNSLKPE DTAMYYCAL**SKCYTRVYDY**WGQGTQVTVSS	1
Anti-CD19 VHH 2	EVQLQESGGGLVQPGGSLRLSCAASGF**IYMV**WVRQAPGK GLEWLS**GIKTERDGVKG**RFTIPRDNAKNTLYLQMNNLKS EDTALYYCAT**EEND**WGQGTQVTVSS	2
Anti-CD19 VHH 3	QVKLEESGGELVQPGGPLRLSCAASGN**IFSINRMG**WYRQA PGKQRAFVA**SITVRGITNYADSVKG**RFTISVDKSKNTIYL QMNALKPEDTAVYYCNA**VSSNRDPDY**WGQGTQVTVSS	3
Anti-BCMA VHH 1	EVQLLESGGGLVQPGGSLRLSCAASGFTFS**SYAMS**WVRQA PGKGLEWVS**SISGSGDYIYYADSVKG**RFTISRDISKNTLY LQMNSLRAEDTAVYYCAK**EGTGANSSLADY**RGQGTLVTVS S	4
Anti-BCMA VHH 2	QVQLVESGGGLVQPGGSLRLSCAASGFTFSS**HAMT**WVRQ APGKGLEWVA**AISGSGDFTHYADSVKG**RFTISRDNSKNTV SLQMNNLRAEDTAVYYCAK**DEDGGSLLGY**RGQGTLVTV SS	5
Anti-BCMA VHH 3	EVQLLESGGGLIQPGGSLRLSCAASGFTFSS**HAMT**WVRQA PGKGLEWVS**AISGSGDYTHYADSVKG**RFTISRDNSKNTVY LQMNSLRAEDSAVYYCAK**DEDGGSLLGH**RGQGTLVTVSS	6
Anti-CD19 scFv 1	DIQMTQTTSSLSASLGDRVTISC**RASQDISKYLN**WYQQK PDGTVKLLIY**HTSRLHS**GVPSRFSGSGSGTDYSLTISNL EQEDIATYFC**QQGNTLPYT**FGGGTKLEIT**GSTSGSGKPG SGEGSTKGEVK**LQESGPGLVAPSQSLSVTCTVSGVSLP**D YGVS**WIRQPPRKGLEWLG**VIWGSETTYYNSALKS**RLTII KDNSKSQVFLKMNSLQTDDTAIYYCAK**HYYYGGSYAMDY** WGQGTSVTVSS	7
Anti-CD19 scFv 2	DVVMTQSPSSIPVTLGESVSISC**RSSKSLQNVNGNTYLY**WF QQRPGQSPQLLIY**RMSNLNS**GVPDRFSGSGSGTDFTLRISG VEPEDVGVYYC**MQHLEYPLT**FGAGTKLEIKGGGGSGGG GSGGGGSQVQLVQSGPELIKPGGSVKMSCKASGYTFT**SYV MH**WVRQKPGQGLEWIG**YINPYNDGTKYNEKFKG**RATLT SDKSSSTAYMELSSLRSEDSAVYYCAR**GTYYYGSRVFDY** WGQGTTVTVSS	8
Anti-CD19 scFv 3	DVVMTQSPSSIPVTLGESVSISC**RSSKSLQNVNGNTYLY**WF QQRPGQSPQLLIY**RMSNLNS**GVPDRESGSGSGTDFTLRISG VEPEDVGVYYC**MQHLEYPLT**FGAGTKLEIK**GGGGSGGG GSGGGGS**QVQLVQSGPELIKPGGSVKMSCKASGYTFT**SYV MH**WVRQKPGQGLEWIG**YINPYNDGTKYNEKFKG**RATLT SDKSSSTAYMELSSLRSEDSAVYYCAR**GTYYYGSRVFDY** WGQGTTVTVSS	9
Anti-BCMA scFv	DIVLTQSPPSLAMSLGKRATISC**RASESVTILGSHLIH**WYQ QKPGQPPTLLIQ**LASNVQT**GVPARFSGSGSRTDFTLTIDPVE EDDVAVYYC**LQSRTIPRT**FGGGTKLEIKGSTSGSGKPGSG EGSTKGQIQLVQSGPELKKPGETVKISCKASGYTFT**DYSIN** WVKRAPGKGLKWMG**WINTETREPAYAYDFRG**RFAFSLE TSASTAYLQINNLKYEDTATYFCAL**DYSYAMDY**WGQGTS VTVSS	10
Anti-BCMA VHH/anti-CD19 scFv	EVQLLESGGGLIQPGGSLRLSCAASGFTFSSHAMTWVRQAP GKGLEWVSAISGSGDYTHYADSVKGRFTISRDNSKNTVYL QMNSLRAEDSAVYYCAKDEDGGSLLGHRGQGTLVTVSS**G GGGSPAG***DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWY QQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQ* EDIATYFCQQGNTLPYTFGGGTKLEIT***GSTSGSGKPGSGEGST KGEVK****LQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPP* *RKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSL QTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS*	11

SEQUENCE TABLE 1-continued

Antibody Sequences.

Description	Sequence (CDRs in boldface and underlined; determined by the Kabat method)	SEQ ID NO
Anti-CD19 VHH/ anti-BCMA scFv	QVKLEESGGELVQPGGPLRLSCAASGNIFSINRMGWYRQA PGKQRAFVASITVRGITNYADSVKGRFTISVDKSKNTIYLQ MNALKPEDTAVYYCNAVSSNRDPDYWGQGTQVTVSS**GG GGSPAG**DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHL IHWYQQKPGQPPTLLIQLASNVQTGVPARFSGSGSRTDFTL TIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK***GSTSGSGK PGSGEGSTKG****QIQLVQSGPELKKPGETVKISCKASGYTFTDYSI NWVKRAPGKGLKWMGWINTETREPAYAYDFRGRFAFSLETSA STAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSS*	12
Anti CD19 scFv/ anti-BCMA VHH	*DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTV KLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQ QGNTLPYTFGGGTKLEIT***GSTSGSGKPGSGEGSTKGEVKL** *QESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEW LGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTAI YYCAKHYYYGGSYAMDYWGQGTSVTVSS***GGGGSPAG**EVQLL ESGGGLIQPGGSLRLSCAASGFTFSSHAMTWVRQAPGKGL EWVSAISGSGDYTHYADSVKGRFTISRDNSKNTVYLQMNS LRAEDSAVYYCAKDEDGGSLLGHRGQGTLVTVSS	71
Anti BCMA scFv/ anti-CD19 VHH	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIHWYQQ KPGQPPTLLIQLASNVQTGVPARFSGSGSRTDFTLTIDPVEE DDVAVYYCLQSRTIPRTFGGGTKLEIK**GSTSGSGKPGSGE GSTKG**QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINW VKRAPGKGLKWMGWINTETREPAYAYDFRGRFAFSLETS ASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVT VSS**GGGGSPAG**QVKLEESGGELVQPGGPLRLSCAASGNIF SINRMGWYRQAPGKQRAFVASITVRGITNYADSVKGRFTIS VDKSKNTIYLQMNALKPEDTAVYYCNAVSSNRDPDYWGQ GTQVTVSS	72
Anti-IFNγ1	VH QVQLVQSGAELKKPGSSVKVSCKASGYIFT**SSWIN**WVKQA PGQGLEWIG**RIDPSDGEVHYNQDFKD**KATLTVDKSTNTA YMELSSLRSEDTAVYYCAR**GFLPWFAD**WGQGTLVTVSS	13
	VL DIQMTQSPSTLSASVGDRVTITCKASENVDTYVSWYQQKP GKAPKLLIYGASNRYTGVPSRFSGSGSGTDFTLTISSLQPDD FATYYCGQSYNYPFTFGQGTKVEVKR	14
Anti-IFNγ scFv1	DIQMTQSPSTLSASVGDRVTITC**KASENVDTYVS**WYQQKP GKAPKLLIY**GASNRYT**GVPSRFSGSGSGTDFTLTISSLQPDD FATYYC**GQSYNYPFT**FGQGTKVEVKR**GGGGSGGGGSGG GGS**QVQLVQSGAELKKPGSSVKVSCKASGYIFT**SSWIN**WV KQAPGQGLEWIG**RIDPSDGEVHYNQDFKD**KATLTVDKST NTAYMELSSLRSEDTAVYYCARG**FLPWFAD**WGQGTLVT VSS	15
Anti-IFNγ2	VH EVQLLESGGGLVQPGGSLRLSCAASGFTFS**SYAMS**WVRQA PGKGLEWVS**AISGSGGSTYYADSVKG**RFTISRDNSKNTLY LQMNSLRAEDTAVYYCAK**DGSSGWYVPHWFDP**WGQGT LVTVSS	16
	VL NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRP GSSPTTVIYEDNQRPSGVPDRESGSIDSSSNSASLTISGLKTE DEADYYCQSYDGSNRWMFGGGTKLTVL	17
Anti-IFNγ scFv2	NFMLTQPHSVSESPGKTVTISC**TRSSGSIASNYVQ**WYQQRP GSSPTTVIY**EDNQRPS**GVPDRESGSIDSSSNSASLTISGLKTE DEADYYC**QSYDGSNRWM**FGGGTKLTVL**GGGGSGGGGS GGGGS**EVQLLESGGGLVQPGGSLRLSCAASGFTES**SYAMS** WVRQAPGKGLEWVSA**ISGSGGSTYYADSVKG**RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAK**DGSSGWYVPHWFDP** WGQGTLVTVSS	18

SEQUENCE TABLE 1-continued

Antibody Sequences.

Description		Sequence (CDRs in boldface and underlined; determined by the Kabat method)	SEQ ID NO
Anti-IFNγ3	VH	EVQLVQSGAEVKKPGESLKISCKGSGYNFT**SYWIG**WVRQ MPGKGLELMG**IIYPGDSDTRYSPSFQG**QVTISADKSISTAY LQWSSLKASDTAMYYCGS**GSYFYFDL**WGRGTLVTVSS	19
	VL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKP GQAPRLLIY**GASSRAT**GIPDRESGSGSGTDFTLTISRLEPEDF AVYYC**QRSGGSSFT**FGPGTKVDIK	20
Anti-IFNγ scFv 3		EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKP GQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQ**RSGGSSFT**FGPGTKVDIKGGGGSGGGGSGGGG SEVQLVQSGAEVKKPGESLKISCKGSGYNFT**SYWIG**WVRQ MPGKGLELMG**IIYPGDSDTRYSPSFQG**QVTISADKSISTAY LQWSSLKASDTAMYYCGS**GSYFYFDL**WGRGTLVTVSS	21
AB1 (anti-IL6R)	VH	EVQLVESGGGLVQPGRSLRLSCAAS**RFTFDDYAMH**WVRQ APGKGLEWVSG**ISWNSGRIGYADSV**KGRFTISRDNAENSL FLQMNGLRAEDTALYYCAK**GRDSFDI**WGQGTMVTVSS	22
	VL	DIQMTQSPSSVSASVGDRVTITC**RASQGISSWLA**WYQQKP GKAPKLLIY**GASSLES**GVPSRFSGSGSGTDFTLTISSLQPEDF ASYYC**QQANSFPYT**FGQGTKLEIK	23
AB2 (anti-IL6)	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFS**PFAMS**WVRQA PGKGLEWVA**KISPGGSWTYYSDTVTG**RFTISRDNAKNSL YLQMNSLRAEDTAVYYCAR**QLWGYYALDI**WGQGTTVTV SS	24
	VL	EIVLTQSPATLSLSPGERATLSC**SASISVSYMY**WYQQKPGQ APRLLIY**DMSNLAS**GIPARFSGSGSGTDFTLTISSLEPEDFAV YYC**MQWSGYPYT**FGGGTKVEIK	25
AB3 (anti-IL6)	VH	EVQLVESGGKLLKPGGSLKLSCAASGFTFS**SFAMS**WFRQSP EKRLEWVA**EISSGGSYTYYPDTVTG**RFTISRDNAKNTLYL EMSSLRSEDTAMYYCAR**GLWGYYALDY**WGQGTSVTVSS	26
	VL	QIVLIQSPAIMSASPGEKVTMTC**SASSSVSYM**YWYQQKPGS SPRLLIY**DTSNLAS**GVPVRESGSGSGTSYSLTISRMEAEDAA TYYC**QQWSGYPYT**FGGGTKLEIK	27
AB4 (anti-IL6R)	VH	QVQLQESGPGLVRPSQTLSLTCTVSGYSIT**SDHAWS**WVRQ PPGRGLEWIG**YISYSGITTYNPSLKS**RVTMLRDTSKNQFSL RLSSVTAADTAVYYCAR**SLARTTAMDY**WGQGSLVTVSS	28
	VL	DIQMTQSPSSLSASVGDRVTITC**RASQDISSYLN**WYQQKPG KAPKLLIY**YTSRLHS**GVPSRFSGSGSGTDFTFTISSLQPEDIA TYYC**QQGNTLPYT**FGQGTKVEIK	29
AB5 (anti-IL6)	VH	EVQLVESGGGLVQPGGSLRLSCAASGFSLS**NYYVT**WVRQA PGKGLEWVG**IIYGSDETAYATSAIG**RFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAR**DDSSDWDAKFNL**WGQGTLVTVS S	30
	VL	AIQMTQSPSSLSASVGDRVTITC**QASQSINNELS**WYQQKPG KAPKLLIY**RASTLAS**GVPSRFSGSGSGTDFTLTISSLQPDDF ATYYC**QQGYSLRNIDNA**FGGGTKVEIK	31
AB6 (anti-gp130)	VH	EVQLVESGGGLVQPGGSLRLSCAASGFNFN**DYFMN**WVRQ APGKGLEWVA**QMRNKNYQYGTYYAESLEG**RFTISRDDS KNSLYLQMNSLKTEDTAVYYCAR**ESYYGFTSY**WGQGTLV TV	32
	VL	DIQMTQSPSSLSASVGDRVTITC**QASQDIGISLS**WYQQKPG KAPKLLIY**NANNLAD**GVPSRFSGSGSGTDFTLTISSLQPEDF ATYYC**LQHNSAPYT**FGQGTKLEIK	33

SEQUENCE TABLE 1-continued

Antibody Sequences.

Description	Sequence (CDRs in boldface and underlined; determined by the Kabat method)	SEQ ID NO
IL6 antagonist scFv 1	DIQMTQSPSSVSASVGDRVTITC**RASQGISSWLA**WYQQKP GKAPKLLIY**GASSLES**GVPSRFSGSGSGTDFTLTISSLQPEDF ASYYC**QQANSFPYT**FGQGTKLEIKGGGGSGGGGSGGGG SEVQLVESGGGLVQPGRSLRLSCAAS**RFTFDDYAMH**WVR QAPGKGLEWVSG**ISWNSGRIGYADSV**KGRFTISRDNAENS LFLQMNGLRAEDTALYYCAK**GRDSFDI**WGQGTMVTVSS	34
IL6 antagonist scFv 2	EIVLTQSPATLSLSPGERATLSC**SASISVSYMY**WYQQKPGQ APRLLIY**DMSNLAS**GIPARFSGSGSGTDFTLTISSLEPEDFAV YYC**MQWSGYPYT**FGGGTKVEIK**GGGGSGGGGSGGGGS** EVQLVESGGGLVQPGGSLRLSCAASGFTFS**PFAMS**WVRQA PGKGLEWVA**KISPGGSWTYYSDTVTG**RFTISRDNAKNSL YLQMNSLRAEDTAVYYCAR**QLWGYYALDI**WGQGTTVTV SS	35
IL6 antagonist scFv 3	QIVLIQSPAIMSASPGEKVTMTC**SASSSVSYM**YWYQQKPGS SPRLLIY**DTSNLAS**GVPVRESGSGSGTSYSLTISRMEAEDAA TYYC**QQWSGYPYT**FGGGTKLEIK**GGGGSGGGGSGGGGS** EVQLVESGGKLLKPGGSLKLSCAASGFTFS**SFAMS**WFRQSP EKRLEWVA**EISSGGSYTYYPDTVTG**RFTISRDNAKNTLYL EMSSLRSEDTAMYYCAR**GLWGYYALDY**WGQGTSVTVSS	36
IL6 antagonist scFv 4	QVQLQESGPGLVRPSQTLSLTCTVSGYSIT**SDHAWS**WVRQ PPGRGLEWIG**YISYSGITTYNPSLKS**RVTMLRDTSKNQFSL RLSSVTAADTAVYYCARSLARTTAMDYWGQGSLVTVSS**G GGGSGGRASGGGGSGGGGS**DIQMTQSPSSLSASVGDRVT ITC**RASQDISSYLN**WYQQKPGKAPKLLIY**YTSRLHS**GVPSR FSGSGSGTDFTFTISSLQPEDIATYYC**QQGNTLPYT**FGQGT KVEIK	37

SEQUENCE TABLE 2

Sequences of Chimeric Antigen Receptor and Components Thereof

Description	Sequence	SEQ ID NO
CD8 transmembrane	IYIWAPLAGTCGVLLLSLVITLYC	38
4-1BB	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	39
Costimulatory domain		
IL-2Rb signaling domain	NCRNTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSS PFPSSSFSPGGLAPEISPLEVLERDKVTQLLPLNTDAYLSLQEL QGQDPTHLV	40
STAT binding motif	YRHQ	41
CD3z signaling domain with STAT binding motif	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGER RRGKGHDGLYQGLSTATKDTYDAYRHQALPPR	42
CD3z signaling domain 1	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGER RRGKGHDGLYQGLSTATKDTYDALHMQALPPR	43
CD8 signal peptide	MALPVTALLLPLALLLHAARP	45
Antibody signal peptide	MKYLLPTAAAGLLLLAAQPAMA	46

SEQUENCE TABLE 2-continued

Sequences of Chimeric Antigen Receptor and Components Thereof

Description	Sequence	SEQ ID NO
Gaussia luciferase signal peptide	MGVKVLFALICIAVAEA	47
human albumin signal peptide	MKWVTFISLLFLESSAYS	48
modified human albumin signal peptide	MKWVTFISLLFLFSSSSRA	49
modified IL2 signal peptide	MRRMQLLLLIALSLALVTNS	50
growth hormone signal peptide	MATGSRTSLLLAFGLLCLPWLQEGSA	51
native IL-IRA signal peptide	MALETIC	52
CD8 hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA CD	53
IL-1RA (mature)	RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGYLQGPNV NLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDETRLQLEA VNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTA MEADQPVSLTNMPDEGVMVTKFYFQEDE	54
IL-1RA 2	***MATGSRTSLLLAFGLLCLPWLQEGSA***RPSGRKSSKMQAFRI WDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIEPHAL FLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSENRKQDKRF AFIRSDSGPTTSFESAACPGWFLCTAMEADQPVSLTNMPDEG VMVTKFYFQEDE	55
IL-1RA 1	***MALETIC***RPSGRKSSKMQAFRIWDVNQKTFYLRNNQLVAGY LQGPNVNLEEKIDVVPIEPHALFLGIHGGKMCLSCVKSGDET RLQLEAVNITDLSENRKQDKRFAFIRSDSGPTTSFESAACPGW FLCTAMEADQPVSLTNMPDEGVMVTKFYFQEDE	56
GS Linker	GGGGSPAG	57
Peptide Linker	SGGGSDPGGGGSGGGGSGGGGSGGGGS	73
Peptide Linker Motif	EAAAK	74
G4S linker	GGGGS	75
$(G4S)_3$	GGGGSGGGGSGGGGS	76
$(G4S)_4$	GGGGSGGGGSGGGGSGGGGS	77
trAPRIL	HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYG VRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFR CIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL SPHGTFLGFVKL	58
trAPRIL/anti-CD19 scFv 1	HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYG VRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFR CIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL SPHGTFLGFVKL**SGGGSDPGGGGSGGGGSGGGGSGGGGS***PAGD IQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVK LLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQ QGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESG PGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIW GSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCA KHYYYGGSYAMDYWGQGTSVTVSS	59

SEQUENCE TABLE 2-continued

Sequences of Chimeric Antigen Receptor and Components Thereof

Description	Sequence	SEQ ID NO
trAPRIL/anti-CD19 scFv 2	HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYG VRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFR CIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL SPHGTFLGFVKL**GGGGSPAG***DIQMTQTTSSLSASLGDRVTISCR ASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGT DYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGSTSGSGK PGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVS WIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFL KMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS	60
trAPRIL/anti-CD19 VHH 1	HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYG VRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFR CIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL SPHGTFLGFVKL**SGGGSDPGGGGSGGGGSGGGGSGGGGS***QVK LEESGGELVQPGGPLRLSCAASGNIFSINRMGWYRQAPGKQRAF VASITVRGITNYADSVKGRFTISVDKSKNTIYLQMNALKPEDT AVYYCNAVSSNRDPDYWGQGTQVTVSS*	61
trAPRIL/anti-CD19 VHH	HSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYG VRIQDAGVYLLYSQVLFQDVTFTMGQVVSREGQGRQETLFR CIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNL SPHGTFLGFVKL**GGGGSPAG***QVKLEESGGELVQPGGPLRLSC AASGNIFSINRMGWYRQAPGKQRAFVASITVRGITNYADSVKGRF TISVDKSKNTIYLQMNALKPEDTAVYYCNAVSSNRDPDYWGQGT QVTVSS*	62
Anti CD19 scFv/anti-BCMAVHH Bispecific CAR	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDG TVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATY FCQQGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVK LQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGL EWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQT DDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS**GGGGSP AG**EVQLLESGGGLIQPGGSLRLSCAASGFTFSSHAMTWVRQ APGKGLEWVSAISGSGDYTHYADSVKGRFTISRDNSKNTVY LQMNSLRAEDSAVYYCAKDEDGGSLLGHRGQGTLVTVSS G *STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELNCRNTGPWLKKVLKCNTPDPSK FFSQLSSEHGGDVQKWLSSPFPSSSFSPGGLAPEISPLEVLERDK VTQLLPLNTDAYLSLQELQGQDPTHLVRVKFSRSADAPAYKQGQ NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD AYRHQALPPR*	44
Anti CD19 scFv/anti-BCMA VHH Bispecific CAR	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLGDRVTISC RASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGS GSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITG STSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVS GVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSR LTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAM DYWGQGTSVTVSS**GGGGSPAG**EVQLLESGGGLIQPGGSLRL SCAASGFTFSSHAMTWVRQAPGKGLEWVSAISGSGDYTHYA DSVKGRFTISRDNSKNTVYLQMNSLRAEDSAVYYCAKDEDG GSLLGHRGQGTLVTVSSGSTTTPAPRPPTPAPTIASQPLSLRPEA *CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKR GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELNCR NTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSS FSPGGLAPEISPLEVLERDKVTQLLPLNTDAYLSLQELQGQDPTH LVRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDAYRHQALPPRSG*	63 64 (no signal peptide)
Anti CD19 VHH/ anti-BCMA scFv Bispecific CAR	QVKLEESGGELVQPGGPLRLSCAASGNIFSINRMGWYRQAP GKQRAFVASITVRGITNYADSVKGRFTISVDKSKNTIYLQMN ALKPEDTAVYYCNAVSSNRDPDYWGQGTQVTVSS**GGGGSP AG**DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIHWYQ QKPGQPPTLLIQLASNVQTGVPARFSGSGSRTDFTLTIDPVEE DDVAVYYCLQSRTIPRTFGGGTKLEIKGSTSGSGKPGSGEGS TKGQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKR APGKGLKWMGWINTETREPAYAYDFRGRFAFSLETSASTAY LQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSSGSTT	78

SEQUENCE TABLE 2-continued

Sequences of Chimeric Antigen Receptor and Components Thereof

Description	Sequence	SEQ ID NO
	TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELNCRNTGPWLKKVLKCNTPDPSKFFS QLSSEHGGDVQKWLSSPFPSSSFSPGGLAPEISPLEVLERDKVTQ LLPLNTDAYLSLQELQGQDPTHLVRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAYRH QALPPR	
Anti CD19 VHH/ anti-BCMA scFv Bispecific CAR	MALPVTALLLPLALLLHAARPQVKLEESGGELVQPGGPLRLSC AASGNIFSINRMGWYRQAPGKQRAFVASITVRGITNYADSVK GRFTISVDKSKNTIYLQMNALKPEDTAVYYCNAVSSNRDPD YWGQGTQVTVSS**GGGGSPAG**DIVLTQSPPSLAMSLGKRATI SCRASESVTILGSHLIHWYQQKPGQPPTLLIQLASNVQTGVPA RFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTK LEIKGSTSGSGKPGSGEGSTKGQIQLVQSGPELKKPGETVKIS CKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYA MDYWGQGTSVTVSSGS*TTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELNCRNT GPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSSFS PGGLAPEISPLEVLERDKVTQLLPLNTDAYLSLQELQGQDPTHLV RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDAYRHQALPPRSG*	65 66 (no signal peptide)
Anti BCMA VHH/ anti-CD19 scFv Bispecific CAR	EVQLLESGGGLIQPGGSLRLSCAASGFTFSSHAMTWVRQAPG KGLEWVSAISGSGDYTHYADSVKGRFTISRDNSKNTVYLQM NSLRAEDSAVYYCAKDEDGGSLLGHRGQGTLVTVSS**GGGG SPAG**DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQ KPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQE DIATYFCQQGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTK GEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPP RKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMN SLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSGST *TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELNCRNTGPWLKKVLKCNTPDPSKF FSQLSSEHGGDVQKWLSSPFPSSSFSPGGLAPEISPLEVLERDKV TQLLPLNTDAYLSLQELQGQDPTHLVRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAY RHQALPPR*	79
Anti BCMA VHH/ anti-CD19 scFv Bispecific CAR	MALPVTALLLPLALLLHAARPEVQLLESGGGLIQPGGSLRLSCA ASGFTFSSHAMTWVRQAPGKGLEWVSAISGSGDYTHYADSV KGRFTISRDNSKNTVYLQMNSLRAEDSAVYYCAKDEDGGSL LGHRGQGTLVTVSS**GGGGSPAG**DIQMTQTTSSLSASLGDRV TISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSR FSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKL EITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTC TVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSAL KSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSY AMDYWGQGTSVTVSSGSTTTPAPRPPTPAPTIASQPLSLRPEAC *RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRG RKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELNCRN TGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSSF SPGGLAPEISPLEVLERDKVTQLLPLNTDAYLSLQELQGQDPTHL VRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDAYRHQALPPRSG*	67 68 (no signal peptide)
Anti BCMA scFv/ anti-CD19 VHH Bispecific CAR	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIHWYQQK PGQPPTLLIQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDD VAVYYCLQSRTIPRTFGGGTKLEIKGSTSGSGKPGSGEGSTK GQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAP GKGLKWMGWINTETREPAYAYDFRGRFAFSLETSASTAYLQ INNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSS**GGGGS PAG**QVKLEESGGELVQPGGPLRLSCAASGNIFSINRMGWYR QAPGKQRAFVASITVRGITNYADSVKGRFTISVDKSKNTIYL QMNALKPEDTAVYYCNAVSSNRDPDYWGQGTQVTVSSGST	80

SEQUENCE TABLE 2-continued

Sequences of Chimeric Antigen Receptor and Components Thereof

Description	Sequence	SEQ ID NO
	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELNCRNTGPWLKKVLKCNTPDPSKF FSQLSSEHGGDVQKWLSSPFPSSSFSPGGLAPEISPLEVLERDKV TQLLPLNTDAYLSLQELQGQDPTHLVRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAY RHQALPPR	
Anti BCMA scFv/ anti-CD19 VHH Bispecific CAR	MALPVTALLLPLALLLHAARPDIVLTQSPPSLAMSLGKRATISC RASESVTILGSHLIHWYQQKPGQPPTLLIQLASNVQTGVPARF SGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLE IKGSTSGSGKPGSGEGSTKGQIQLVQSGPELKKPGETVKISCK ASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYAYD FRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMD YWGQGTSVTVSS**GGGGSPAG**QVKLEESGGELVQPGGPLRL SCAASGNIFSINRMGWYRQAPGKQRAFVASITVRGITNYADS VKGRFTISVDKSKNTIYLQMNALKPEDTAVYYCNAVSSNRD PDYWGQGTQVTVSSGS*TTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELNCRNT GPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSSFS PGGLAPEISPLEVLERDKVTQLLPLNTDAYLSLQELQGQDPTHLV RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDAYRHQALPPRSG*	69 70 (no signal peptide)

SEQUENCE TABLE 3

Sequences for Guide RNAs Targeting IFNγ

Description	Sequence	SEQ ID NO
IFNγ exon 1 target site 1 (PAM)	GAAATATACAAGTTATATCT (TGG)	81
sgRNA spacer for target site 1	GAAAUAUACAAGUUAUAUCU	82
sgRNA for target site 1	G**AAAUAUACAAGUUAUAUCU**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	83
IFNγ exon 1 target site 2 (PAM)	TTTCAGCTCTGCATCGTTT (TGG)	84
sgRNA space for target site 2	UUUCAGCUCUGCAUCGUUU	85
sgRNA for target site 2	G**UUUCAGCUCUGCAUCGUUU**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	86
IFNγ exon 1 target site 3 (PAM)	TTCAGCTCTGCATCGTTTT (GGG)	87
sgRNA space for target site 3	UUCAGCUCUGCAUCGUUUU	88
sgRNA for target site 3	G**UUCAGCUCUGCAUCGUUUU**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	89

SEQUENCE TABLE 3-continued

Sequences for Guide RNAs Targeting IFNγ

Description	Sequence	SEQ ID NO
IFNγ exon 1 target site 4 (PAM)	GCATCGTTTTGGGTTCTCT (TGG)	90
sgRNA space for target site 4	GCAUCGUUUUGGGUUCUCU	91
sgRNA for target site 4	**GCAUCGUUUUGGGUUCUCU**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	92
IFNγ exon 1 target site 5 (PAM)	TCTCTTGGCTGTTACTGCC (AGG)	93
sgRNA space for target site 5	UCUCUUGGCUGUUACUGCC	94
sgRNA for target site 5	**GUCUCUUGGCUGUUACUGCC**GUUUUAGAGCUAGAAAU AGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAA AAAGUGGCACCGAGUCGGUGCUUUU	95
IFNγ exon 1 target site 6 (PAM)	TTCTTTTACATATGGGTCC (TGG)	96
sgRNA space for target site 6	UUCUUUUACAUAUGGGUCC	97
sgRNA for target site 6	**GUUCUUUUACAUAUGGGUCC**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	98
IFNγ exon 1 target site 7 (PAM)	TTCTGCTTCTTTTACATAT (GGG)	99
sgRNA space for target site 7	UUCUGCUUCUUUUACAUAU	100
sgRNA for target site 7	**GUUCUGCUUCUUUUACAUAU**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	101
IFNγ exon 1 target site 8 (PAM)	TTTCTGCTTCTTTTACATA (TGG)	102
sgRNA space for target site 8	UUUCUGCUUCUUUUACAUA	103
sgRNA for target site 8	**GUUUCUGCUUCUUUUACAUA**GUUUUAGAGCUAGAAAUA GCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAA AAGUGGCACCGAGUCGGUGCUUUU	104

EXAMPLES

Example 1: Preparation of Genetically Engineered T Cells Expressing Bi-Specific Chimeric Antigen Receptor (CAR)

[0174] Blood samples were collected from human patient donors and the peripheral blood mononuclear cells (PBMCs) were isolated from the blood samples via routine practice. Lentiviral expression vectors coding for an anti-CD19/anti-BCMA bispecific CAR, and optionally an anti-IFNγ scFv (SEQ ID NO: 21 or SEQ ID NO: 18) and/or an anti-IL6 scFv (SEQ ID NO: 35) were introduced into the PBMCs to allow for expression of the bispecific CAR and optionally the anti-IFNγ scFv and the anti-IL6 scFv.

[0175] Two designs of the anti-CD19/anti-BCMA bispecific CAR were explored: (a) anti-CD19 VHH/anti-BCMA scFv, and (b) anti-BCMA VHH/anti-CD19 scFv. All of the bispecific CAR constructs contain the CD8 lead sequence (SEQ ID NO: 45), the GS linker (SEQ ID NO: 57), the CD8 hinge domain (SEQ ID NO: 53), the CD8 transmembrane domain (SEQ ID NO: 38), the 4-1BB co-stimulatory domain (SEQ ID NO: 39), the IL-2Rb signaling domain (SEQ ID NO: 40), and the CD3z signaling domain (SEQ ID NO: 42). See Sequence Table 2. The construct of (a) comprises the

amino acid sequence of SEQ ID NO: 65; the construct of (b) comprises the amino acid sequence of SEQ ID NO: 67.

[0176] In some instances, a bicistronic expression vector comprising the coding sequence of construct (a) or (b) and the coding sequence of an anti-IFNγ scFv (SEQ ID NO: 21 or SEQ ID NO: 18) connected by a T2A-coding sequence linker was used to produce genetically engineered T cells expressing both the bi-specific CAR and the anti-IFNγ scFv (secretive). In other instances, a tricistronic expression vector comprising the coding sequence of construct (a) or (b), the coding sequence of an anti-IFNγ scFv (SEQ ID NO: 21 or SEQ ID NO: 18) connected to the coding sequence of (a) or (b) by a T2A-coding sequence, and the coding sequence of the anti-IL6 scFv (SEQ ID NO:35) connected to the coding sequence of an anti-IFNγ scFv via a P2A-coding sequence.

[0177] Primary T cells collected from healthy donors were activated by anti-CD3/CD28 beads (Thermo scientific). One day later, the T cells were transduced with the lentiviral vectors encoding one of the above-noted bi-specific CAR and optionally the anti-IFNγ scFv and the anti-IL6 scFv disclosed above. The transduced cells were expanded and tested for CD3 expression by FACS analysis and the CD3+ population was gated for further analysis.

[0178] CAR expression was analyzed by flow cytometry using a biotinylated primary antibody recognizing the antibody fragment in the CAR and a fluorescence labeled secondary antibody conjugated with Streptavidin.

[0179] Functionality of the bi-specific Car-T cells was analyzed by coculture of the CAR-T cells with target antigen-presenting cells (APCs) or target tumor cells to evaluate CAR-T cell proliferation, cytotoxicity, or a combination thereof.

Example 2: Treating Acute Lymphocytic Leukemia (ALL) Patient with Anti-CD19/Anti-BCMA Bi-Specific CAR-T Cells

[0180] Human patients having acute lymphocytic leukemia (ALL) were treated with the bi-specific CAR-T cells as detailed below.

(A) Treatment with Bi-Specific CAR T Cells Secreting Anti-IFNγ scFv

[0181] A patient (ALL Patient 1) diagnosed with refractory and relapsed acute lymphocytic leukemia (ALL) was administered via intravenous infusion, bi-specific CAR T cells (anti-BCMA VHH/anti-CD19 scFv, see design (b) in Example 1) secreting only the exemplary anti-IFNγ scFv (see Example 1 above, comprising the amino acid sequence of SEQ ID NO: 21) at a dose of 0.4×10^8 CAR+ T cells, after a standard lymphodepletion treatment.

[0182] After the treatment, blood samples were collected from the patient. A significant expansion of the CAR-T cells was detected over time (FIG. **2**A) and low levels of IFNγ were detected (FIG. **2**B) in the blood samples. This result suggest that the bispecific anti-CD19/BCMA CAR-T cells, which co-express the anti-IFNγ scFv, are sufficient to induce durable CAR+ T cell expansion. This patient showed complete response in clinical efficacy. During this treatment, only grade 2 CRS was observed.

(B) Treatment with Bi-Specific CAR-T Cells Secreting Both Anti-IL6 scFv and Anti-IFNγ scFv

[0183] A patient (ALL Patient 2) diagnosed with ALL were administered via intravenous infusion the bi-specific CAR-T cells (anti-BCMA VHH/anti-CD19 scFv, see design (b) in Example 1) expressing both the anti-IL6 scFv and the anti-IFNγ scFv comprising the amino acid sequence of disclosed in Example 1 above. This patient showed complete response in clinical efficacy. During this treatment, only grade 1 CRS was observed. Similar to Patient 1, Patient 2 also showed low levels of IFNγ in blood samples after the treatment (FIG. **2**C).

Example 3: Treating Multiple Myeloma (MM) Patients with Bi-Specific Anti-CD19/Anti-BCMA CAR-T Cells

[0184] Up to 3 patients (MM Patient 1, MM Patient 2, and MM Patient 3) diagnosed with refractory and relapsed MM was administered CAR-T cells co-expressing the bispecific CAR construct (a) and the anti-IFNγ scFv comprising the amino acid sequence of SEQ ID NO: 21 as disclosed in Example 1 above via intravenous infusion (Patient 1, 0.4×10^8, Patient 2, 0.8×10^8; Patient 3, 0.8×10^8 CAR+ T cells). One patient (MM Patient 4) diagnosed with refractory and relapsed MM was administered CAR-T cells expressing the bispecific CAR construct (a) but not the anti-IFNγ scFv.

[0185] Following the treatment, CAR+ T cell expansion and levels of IFNγ were determined in each of the MM patient. Significant expansion of CAR+ T cells was detected in all of the MM patients treated in this example. FIGS. **3**A and **3**C-**3**D. Low levels of IFNγ were also detected in the peripheral blood of the patients treated with CAR-T cells expressing both the bispecific CAR and the anti-IFNγ scFv. See FIG. **3**B for data from one representative patient. This indicates that the bi-specific anti-CD19/BCMA CAR-T cells co-expressing the anti-IFNγ scFv are capable of inducing robust CAR+ T cell expansion. The MM patients treated with the co-expressing the bispecific CAR and the anti-IFNγ scFv achieved complete response (CR) after the treatment. Although bone marrow examination detected 79.5% aberrant plasma cells in patient 1 before treatment, there was only transient mild hypotension during treatment successfully resolved by 10 mg of Norepinephrine in 1 day, and therefore grade 3 CRS observed. During this treatment in patient 2 and patient 3, only grade 1 CRS was observed.

[0186] CAR-T cell expansion was also observed in the MM patient treated with the T cells expressing the bi-specific CAR but not the anti-IFNγ scFv. FIG. **3**E. Clinical response of this patient is under evaluation. During this treatment, only grade 1 CRS was observed.

Example 4: In Vitro Cytotoxicity Assay of Bi-Specific CAR-T Cells

[0187] The in vitro cytotoxicity of CAR-T cells co-expressing the bispecific CAR construct (a) and the anti-IFNγ scFv disclosed in Example 1 above (SEQ ID NO: 21), and CAR-T cells expressing only the bispecific CAR construct (a) was evaluated in this example.

[0188] Human T cells were activated and transduced to generate genetically engineered T cells expressing both the bi-specific CAR and the anti-IFNγ scFv, or only the bi-specific CAR. The resulting engineered T cells were incubated with target tumor cells expressing green fluorescent protein (GFP, as a reporter) at various effector to target (E:T) ratios. Killing efficacy was assessed by flow cytometry by counting the number of live GFP+ target cells, which is in inverse correlation to the level of cytotoxicity. As shown in FIGS. **4**A-**4**C, both types of CAR-T cells showed certain

levels of cytotoxicity against Nalm6 cells (B cell precursor leukemia cells), MM1S cells (multiple myeloma cells), and RPMI 8226 cells (plasmacytoma cells). Co-expression of the anti-IFNγ scFv did not show significant impact on the CAR-T cell cytotoxicity against the MM1S cells and RPMI 8226 cells; however, it was found to reduce the cytotoxicity against Nalm6 cells. See FIG. **4**A relative to FIGS. **4**B and **4**C.

Other Embodiments

[0189] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[0190] From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

EQUIVALENTS

[0191] While several inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

[0192] All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

[0193] All references, patents and patent applications disclosed herein are incorporated by reference with respect to the subject matter for which each is cited, which in some cases may encompass the entirety of the document.

[0194] The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

[0195] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0196] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[0197] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[0198] It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

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Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Asp Ser
        35 40 45

Trp Thr Asp Ala Val Lys Gly Arg Phe Ala Ile Ser Gln Asp Asn Ala
    50 55 60

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr
65 70 75 80

Ala Met Tyr Tyr Cys Ala Leu Ser Lys Cys Tyr Thr Arg Val Tyr Asp
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Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu Ser Gly Ile Lys
        35 40 45

Thr Glu Arg Asp Gly Val Lys Gly Arg Phe Thr Ile Pro Arg Asp Asn
    50 55 60

Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Asn Leu Lys Ser Glu Asp
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Thr Gln Val Thr Val Ser Ser
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Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn
            20                  25                  30

Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val
        35                  40                  45

Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln
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Val Thr Val Ser Ser
        115


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            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Gly Ser Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Glu Gly Thr Gly Ala Asn Ser Ser Leu Ala Asp Tyr Arg Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
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1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ala Ile Ser Gly Ser Gly Asp Phe Thr His Tyr Ala Asp Ser Val
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    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Ser
65                  70                  75                  80

Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly Tyr Arg Gly Gln Gly
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Thr Leu Val Thr Val Ser Ser
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            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

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Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
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145                 150                 155                 160

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                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
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Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
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Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Asn Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65                  70                  75                  80

Ser Gly Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
                85                  90                  95

Leu Glu Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Gln Leu Val Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Gly Ser
    130                 135                 140

Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val
145                 150                 155                 160

Met His Trp Val Arg Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly
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Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Asn Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65                  70                  75                  80

Ser Gly Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
                85                  90                  95

Leu Glu Tyr Pro Ile Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Gln Leu Val Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Gly Ser
    130                 135                 140

Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val
145                 150                 155                 160

Met His Trp Val Arg Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly
                165                 170                 175

Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys
            180                 185                 190

Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met
        195                 200                 205

Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln
225                 230                 235                 240

Gly Thr Thr Val Thr Val Ser Ser
                245
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<210> SEQ ID NO 10
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 10

Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1 5 10 15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
115 120 125

Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly
130 135 140

Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
145 150 155 160

Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp
165 170 175

Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp
180 185 190

Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala
195 200 205

Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe
210 215 220

Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225 230 235 240

Ser Val Thr Val Ser Ser
245

<210> SEQ ID NO 11
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 11

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp
        115                 120                 125

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
    130                 135                 140

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
145                 150                 155                 160

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
                165                 170                 175

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180                 185                 190

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
        195                 200                 205

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
    210                 215                 220

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly Ser
225                 230                 235                 240

Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys Leu
                245                 250                 255

Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val
            260                 265                 270

Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp
        275                 280                 285

Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp
    290                 295                 300

Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr
305                 310                 315                 320

Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser
                325                 330                 335

Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr
            340                 345                 350

Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
        355                 360                 365

Thr Val Ser Ser
    370


<210> SEQ ID NO 12
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 12

Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly
1               5                   10                  15

Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn
            20                  25                  30

Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val
        35                  40                  45
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Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp Ile Val
        115                 120                 125

Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly Lys Arg Ala
    130                 135                 140

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu Gly Ser His
145                 150                 155                 160

Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Thr Leu Leu
                165                 170                 175

Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala Arg Phe Ser
            180                 185                 190

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu
        195                 200                 205

Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg Thr Ile Pro
    210                 215                 220

Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Ser Thr Ser
225                 230                 235                 240

Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Gln Ile
                245                 250                 255

Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val
            260                 265                 270

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Ser Ile
        275                 280                 285

Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe Arg Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Gln
                325                 330                 335

Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Leu
            340                 345                 350

Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
        355                 360                 365

Val Ser Ser
    370


<210> SEQ ID NO 13
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 13

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ser
1               5                   10                  15
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Ser Ser
            20                  25                  30

Trp Ile Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Ser Asp Gly Glu Val His Tyr Asn Gln Asp Phe
    50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Phe Leu Pro Trp Phe Ala Asp Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 14
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 14

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asn Val Asp Thr Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Ser Tyr Asn Tyr Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg
            100                 105


<210> SEQ ID NO 15
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 15

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asn Val Asp Thr Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Ser Tyr Asn Tyr Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Gly Gly Gly Gly
            100                 105                 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
        115                 120                 125

Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ser Ser Val Lys Val Ser
    130                 135                 140

Cys Lys Ala Ser Gly Tyr Ile Phe Thr Ser Ser Trp Ile Asn Trp Val
145                 150                 155                 160

Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Asp Pro
                165                 170                 175

Ser Asp Gly Glu Val His Tyr Asn Gln Asp Phe Lys Asp Lys Ala Thr
            180                 185                 190

Leu Thr Val Asp Lys Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser
        195                 200                 205

Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Phe Leu
    210                 215                 220

Pro Trp Phe Ala Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240


<210> SEQ ID NO 16
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 16

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Gly Ser Ser Gly Trp Tyr Val Pro His Trp Phe Asp Pro
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 17
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 17
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Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
            20                  25                  30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
        35                  40                  45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly
                85                  90                  95

Ser Asn Arg Trp Met Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 18
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
            20                  25                  30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
        35                  40                  45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly
                85                  90                  95

Ser Asn Arg Trp Met Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
        115                 120                 125

Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
    130                 135                 140

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
145                 150                 155                 160

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
                165                 170                 175

Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
        195                 200                 205

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220

Asp Gly Ser Ser Gly Trp Tyr Val Pro His Trp Phe Asp Pro Trp Gly
225                 230                 235                 240
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Gln Gly Thr Leu Val Thr Val Ser Ser
245

<210> SEQ ID NO 19
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 19

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Leu Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Gly Ser Gly Ser Tyr Phe Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 20
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 20

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Ser Gly Gly Ser Ser
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 21
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 21

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Ser Gly Gly Ser Ser
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Gly
100 105 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
115 120 125

Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser
130 135 140

Cys Lys Gly Ser Gly Tyr Asn Phe Thr Ser Tyr Trp Ile Gly Trp Val
145 150 155 160

Arg Gln Met Pro Gly Lys Gly Leu Glu Leu Met Gly Ile Ile Tyr Pro
165 170 175

Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr
180 185 190

Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser
195 200 205

Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Gly Ser Gly Ser Tyr
210 215 220

Phe Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
225 230 235 240

<210> SEQ ID NO 22
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 22

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Gly Arg Asp Ser Phe Asp Ile Trp Gly Gln Gly Thr Met Val

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            100                 105                 110

Thr Val Ser Ser
        115


<210> SEQ ID NO 23
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 23

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 24
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 24

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Pro Phe
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Lys Ile Ser Pro Gly Gly Ser Trp Thr Tyr Tyr Ser Asp Thr Val
    50                  55                  60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gln Leu Trp Gly Tyr Tyr Ala Leu Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser
        115


<210> SEQ ID NO 25
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 25

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ile Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
35 40 45

Asp Met Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65 70 75 80

Asp Phe Ala Val Tyr Tyr Cys Met Gln Trp Ser Gly Tyr Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 26
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 26

Glu Val Gln Leu Val Glu Ser Gly Gly Lys Leu Leu Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ala Met Ser Trp Phe Arg Gln Ser Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Glu Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Thr Val
50 55 60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Glu Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Trp Gly Tyr Tyr Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> SEQ ID NO 27
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 27

Gln Ile Val Leu Ile Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr

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        35                  40                  45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Gly Tyr Pro Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 28
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 28

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Ser Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 29
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95
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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 30
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Asn Tyr
20 25 30

Tyr Val Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Tyr Gly Ser Asp Glu Thr Ala Tyr Ala Thr Ser Ala Ile
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Asp Asp Ser Ser Asp Trp Asp Ala Lys Phe Asn Leu Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 31
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 31

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Asn Asn Glu
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Arg Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Ser Leu Arg Asn
85 90 95

Ile Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 32
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Asn Asp Tyr
20 25 30

Phe Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Met Arg Asn Lys Asn Tyr Gln Tyr Gly Thr Tyr Tyr Ala Glu
50 55 60

Ser Leu Glu Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Glu Ser Tyr Tyr Gly Phe Thr Ser Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val
115

<210> SEQ ID NO 33
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Gly Ile Ser
20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asn Ala Asn Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Ala Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 34
<211> LENGTH: 238
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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Tyr Gly Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
        115                 120                 125

Ser Gly Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys
    130                 135                 140

Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg
145                 150                 155                 160

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn
                165                 170                 175

Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
            180                 185                 190

Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe Leu Gln Met Asn Gly Leu
        195                 200                 205

Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Lys Gly Arg Asp Ser
    210                 215                 220

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
225                 230                 235


<210> SEQ ID NO 35
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 35

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ile Ser Val Ser Tyr Met
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        35                  40                  45

Asp Met Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65                  70                  75                  80

Asp Phe Ala Val Tyr Tyr Cys Met Gln Trp Ser Gly Tyr Pro Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
        115                 120                 125

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala
    130                 135                 140

Ala Ser Gly Phe Thr Phe Ser Pro Phe Ala Met Ser Trp Val Arg Gln
145                 150                 155                 160
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Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Lys Ile Ser Pro Gly Gly
                165                 170                 175

Ser Trp Thr Tyr Tyr Ser Asp Thr Val Thr Gly Arg Phe Thr Ile Ser
            180                 185                 190

Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg
        195                 200                 205

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gln Leu Trp Gly Tyr
    210                 215                 220

Tyr Ala Leu Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
225                 230                 235                 240


<210> SEQ ID NO 36
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 36

Gln Ile Val Leu Ile Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr
        35                  40                  45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Gly Tyr Pro Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
        115                 120                 125

Gly Gly Lys Leu Leu Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
    130                 135                 140

Ala Ser Gly Phe Thr Phe Ser Ser Phe Ala Met Ser Trp Phe Arg Gln
145                 150                 155                 160

Ser Pro Glu Lys Arg Leu Glu Trp Val Ala Glu Ile Ser Ser Gly Gly
                165                 170                 175

Ser Tyr Thr Tyr Tyr Pro Asp Thr Val Thr Gly Arg Phe Thr Ile Ser
            180                 185                 190

Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Glu Met Ser Ser Leu Arg
        195                 200                 205

Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Leu Trp Gly Tyr
    210                 215                 220

Tyr Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
225                 230                 235                 240


<210> SEQ ID NO 37
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 37

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Ser Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
130 135 140

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
145 150 155 160

Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr Gln
165 170 175

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180 185 190

Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195 200 205

Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr
210 215 220

Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly
225 230 235 240

Thr Lys Val Glu Ile Lys
245

<210> SEQ ID NO 38
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 38

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> SEQ ID NO 39
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 39

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> SEQ ID NO 40
<211> LENGTH: 94
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 40

Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val Leu Lys Cys Asn
1 5 10 15

Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser Ser Glu His Gly
20 25 30

Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro Ser Ser Ser Phe
35 40 45

Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu Glu Val Leu Glu
50 55 60

Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn Thr Asp Ala Tyr Leu
65 70 75 80

Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His Leu Val
85 90

<210> SEQ ID NO 41
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 41

Tyr Arg His Gln
1

<210> SEQ ID NO 42
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

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Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu Pro Pro Arg
100 105 110

<210> SEQ ID NO 43
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> SEQ ID NO 44
<211> LENGTH: 691
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
100 105 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
115 120 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
130 135 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser

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145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Glu Val Gln
                245                 250                 255

Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly Ser Leu Arg
            260                 265                 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His Ala Met Thr
        275                 280                 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile
    290                 295                 300

Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val Lys Gly Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln Met
                325                 330                 335

Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys Ala Lys Asp
            340                 345                 350

Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly Thr Leu Val
        355                 360                 365

Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    370                 375                 380

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
385                 390                 395                 400

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
                405                 410                 415

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
            420                 425                 430

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
        435                 440                 445

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    450                 455                 460

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
465                 470                 475                 480

Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys
                485                 490                 495

Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu
            500                 505                 510

Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe
        515                 520                 525

Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro
    530                 535                 540

Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn
545                 550                 555                 560
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Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr
                565                 570                 575

His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
            580                 585                 590

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
        595                 600                 605

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
    610                 615                 620

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
625                 630                 635                 640

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
                645                 650                 655

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
            660                 665                 670

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu
        675                 680                 685

Pro Pro Arg
    690


<210> SEQ ID NO 45
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 45

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro
            20


<210> SEQ ID NO 46
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

Met Lys Tyr Leu Leu Pro Thr Ala Ala Ala Gly Leu Leu Leu Leu Ala
1               5                   10                  15

Ala Gln Pro Ala Met Ala
            20


<210> SEQ ID NO 47
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 47

Met Gly Val Lys Val Leu Phe Ala Leu Ile Cys Ile Ala Val Ala Glu
1               5                   10                  15

Ala
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-continued

<210> SEQ ID NO 48
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 48

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> SEQ ID NO 49
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 49

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ser
1 5 10 15

Ser Arg Ala

<210> SEQ ID NO 50
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

Met Arg Arg Met Gln Leu Leu Leu Leu Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser
20

<210> SEQ ID NO 51
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 51

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu
1 5 10 15

Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala
20 25

<210> SEQ ID NO 52
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52

Met Ala Leu Glu Thr Ile Cys
1 5

<210> SEQ ID NO 53

-continued

<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
            20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
        35 40 45

<210> SEQ ID NO 54
<211> LENGTH: 152
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

Arg Pro Ser Gly Arg Lys Ser Ser Lys Met Gln Ala Phe Arg Ile Trp
1 5 10 15

Asp Val Asn Gln Lys Thr Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala
            20 25 30

Gly Tyr Leu Gln Gly Pro Asn Val Asn Leu Glu Glu Lys Ile Asp Val
        35 40 45

Val Pro Ile Glu Pro His Ala Leu Phe Leu Gly Ile His Gly Gly Lys
    50 55 60

Met Cys Leu Ser Cys Val Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu
65 70 75 80

Glu Ala Val Asn Ile Thr Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys
                85 90 95

Arg Phe Ala Phe Ile Arg Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu
            100 105 110

Ser Ala Ala Cys Pro Gly Trp Phe Leu Cys Thr Ala Met Glu Ala Asp
        115 120 125

Gln Pro Val Ser Leu Thr Asn Met Pro Asp Glu Gly Val Met Val Thr
    130 135 140

Lys Phe Tyr Phe Gln Glu Asp Glu
145 150

<210> SEQ ID NO 55
<211> LENGTH: 178
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu
1 5 10 15

Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Arg Pro Ser Gly Arg Lys
            20 25 30

Ser Ser Lys Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr
        35 40 45

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Phe Tyr Leu Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro
    50                  55                  60

Asn Val Asn Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His
65                  70                  75                  80

Ala Leu Phe Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val
                85                  90                  95

Lys Ser Gly Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr
            100                 105                 110

Asp Leu Ser Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg
        115                 120                 125

Ser Asp Ser Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly
    130                 135                 140

Trp Phe Leu Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr
145                 150                 155                 160

Asn Met Pro Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu
                165                 170                 175

Asp Glu
```

<210> SEQ ID NO 56
<211> LENGTH: 159
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

```
Met Ala Leu Glu Thr Ile Cys Arg Pro Ser Gly Arg Lys Ser Ser Lys
1               5                   10                  15

Met Gln Ala Phe Arg Ile Trp Asp Val Asn Gln Lys Thr Phe Tyr Leu
            20                  25                  30

Arg Asn Asn Gln Leu Val Ala Gly Tyr Leu Gln Gly Pro Asn Val Asn
        35                  40                  45

Leu Glu Glu Lys Ile Asp Val Val Pro Ile Glu Pro His Ala Leu Phe
    50                  55                  60

Leu Gly Ile His Gly Gly Lys Met Cys Leu Ser Cys Val Lys Ser Gly
65                  70                  75                  80

Asp Glu Thr Arg Leu Gln Leu Glu Ala Val Asn Ile Thr Asp Leu Ser
                85                  90                  95

Glu Asn Arg Lys Gln Asp Lys Arg Phe Ala Phe Ile Arg Ser Asp Ser
            100                 105                 110

Gly Pro Thr Thr Ser Phe Glu Ser Ala Ala Cys Pro Gly Trp Phe Leu
        115                 120                 125

Cys Thr Ala Met Glu Ala Asp Gln Pro Val Ser Leu Thr Asn Met Pro
    130                 135                 140

Asp Glu Gly Val Met Val Thr Lys Phe Tyr Phe Gln Glu Asp Glu
145                 150                 155
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<210> SEQ ID NO 57
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

-continued

Gly Gly Gly Gly Ser Pro Ala Gly
1 5

<210> SEQ ID NO 58
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 58

His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp
1 5 10 15

Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg
20 25 30

Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val
35 40 45

Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met
50 55 60

Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe
65 70 75 80

Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser
85 90 95

Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser
100 105 110

Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly
115 120 125

Thr Phe Leu Gly Phe Val Lys Leu
130 135

<210> SEQ ID NO 59
<211> LENGTH: 411
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59

His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp
1 5 10 15

Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg
20 25 30

Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val
35 40 45

Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met
50 55 60

Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe
65 70 75 80

Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser
85 90 95

Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser
100 105 110

Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly
115 120 125

Thr Phe Leu Gly Phe Val Lys Leu Ser Gly Gly Gly Ser Asp Pro Gly
130 135 140

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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Pro Ala Gly Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
                165                 170                 175

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
            180                 185                 190

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
        195                 200                 205

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
    210                 215                 220

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
225                 230                 235                 240

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
                245                 250                 255

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            260                 265                 270

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
        275                 280                 285

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
    290                 295                 300

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
305                 310                 315                 320

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
                325                 330                 335

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
            340                 345                 350

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
        355                 360                 365

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
    370                 375                 380

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
385                 390                 395                 400

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
                405                 410


<210> SEQ ID NO 60
<211> LENGTH: 389
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 60

His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp
1               5                   10                  15

Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg
            20                  25                  30

Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val
        35                  40                  45

Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met
    50                  55                  60

Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe
65                  70                  75                  80
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Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser
                85                  90                  95

Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser
            100                 105                 110

Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly
        115                 120                 125

Thr Phe Leu Gly Phe Val Lys Leu Gly Gly Gly Gly Ser Pro Ala Gly
    130                 135                 140

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
145                 150                 155                 160

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
                165                 170                 175

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
            180                 185                 190

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
        195                 200                 205

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
    210                 215                 220

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
225                 230                 235                 240

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
                245                 250                 255

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
            260                 265                 270

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
        275                 280                 285

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
    290                 295                 300

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
305                 310                 315                 320

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
                325                 330                 335

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
            340                 345                 350

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
        355                 360                 365

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
    370                 375                 380

Val Thr Val Ser Ser
385


<210> SEQ ID NO 61
<211> LENGTH: 280
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61

His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp
1               5                   10                  15

Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg
            20                  25                  30
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Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val
        35                  40                  45

Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met
    50                  55                  60

Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe
65                  70                  75                  80

Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser
                85                  90                  95

Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser
            100                 105                 110

Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly
        115                 120                 125

Thr Phe Leu Gly Phe Val Lys Leu Ser Gly Gly Gly Ser Asp Pro Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln
                165                 170                 175

Pro Gly Gly Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe
            180                 185                 190

Ser Ile Asn Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
        195                 200                 205

Ala Phe Val Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp
    210                 215                 220

Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr
225                 230                 235                 240

Ile Tyr Leu Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr
                245                 250                 255

Tyr Cys Asn Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln
            260                 265                 270

Gly Thr Gln Val Thr Val Ser Ser
        275                 280


<210> SEQ ID NO 62
<211> LENGTH: 261
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62

His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp
1               5                   10                  15

Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg
            20                  25                  30

Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val
        35                  40                  45

Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met
    50                  55                  60

Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe
65                  70                  75                  80

Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser
                85                  90                  95
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Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser
            100                 105                 110

Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly
        115                 120                 125

Thr Phe Leu Gly Phe Val Lys Leu Gly Gly Gly Gly Ser Pro Ala Gly
    130                 135                 140

Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly
145                 150                 155                 160

Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn
                165                 170                 175

Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val
            180                 185                 190

Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys
        195                 200                 205

Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu
    210                 215                 220

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
225                 230                 235                 240

Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln
                245                 250                 255

Val Thr Val Ser Ser
            260


<210> SEQ ID NO 63
<211> LENGTH: 714
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
    50                  55                  60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
    130                 135                 140

Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro
145                 150                 155                 160

Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro
                165                 170                 175
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Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu
            180                 185                 190

Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala
        195                 200                 205

Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val
    210                 215                 220

Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr
225                 230                 235                 240

Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp
                245                 250                 255

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro
            260                 265                 270

Ala Gly Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro
        275                 280                 285

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    290                 295                 300

Ser His Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
305                 310                 315                 320

Trp Val Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp
                325                 330                 335

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
            340                 345                 350

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr
        355                 360                 365

Tyr Cys Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly
    370                 375                 380

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala
385                 390                 395                 400

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
                405                 410                 415

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
            420                 425                 430

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
        435                 440                 445

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
    450                 455                 460

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
465                 470                 475                 480

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
                485                 490                 495

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly
            500                 505                 510

Pro Trp Leu Lys Lys Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys
        515                 520                 525

Phe Phe Ser Gln Leu Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp
    530                 535                 540

Leu Ser Ser Pro Phe Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala
545                 550                 555                 560

Pro Glu Ile Ser Pro Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln
                565                 570                 575
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Leu Leu Pro Leu Asn Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln
            580                 585                 590

Gly Gln Asp Pro Thr His Leu Val Arg Val Lys Phe Ser Arg Ser Ala
        595                 600                 605

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    610                 615                 620

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
625                 630                 635                 640

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                645                 650                 655

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            660                 665                 670

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        675                 680                 685

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr
    690                 695                 700

Arg His Gln Ala Leu Pro Pro Arg Ser Gly
705                 710


<210> SEQ ID NO 64
<211> LENGTH: 693
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 64

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205
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Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Glu Val Gln
                245                 250                 255

Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly Ser Leu Arg
            260                 265                 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His Ala Met Thr
        275                 280                 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile
    290                 295                 300

Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val Lys Gly Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln Met
                325                 330                 335

Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys Ala Lys Asp
            340                 345                 350

Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly Thr Leu Val
        355                 360                 365

Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    370                 375                 380

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
385                 390                 395                 400

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
                405                 410                 415

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
            420                 425                 430

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
        435                 440                 445

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    450                 455                 460

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
465                 470                 475                 480

Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys
                485                 490                 495

Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu
            500                 505                 510

Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe
        515                 520                 525

Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro
    530                 535                 540

Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn
545                 550                 555                 560

Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr
                565                 570                 575

His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
            580                 585                 590

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
        595                 600                 605

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
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    610                 615                 620

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
625                 630                 635                 640

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
                645                 650                 655

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
            660                 665                 670

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu
        675                 680                 685

Pro Pro Arg Ser Gly
    690


<210> SEQ ID NO 65
<211> LENGTH: 713
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu
            20                  25                  30

Val Gln Pro Gly Gly Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn
        35                  40                  45

Ile Phe Ser Ile Asn Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gln Arg Ala Phe Val Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr
65                  70                  75                  80

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys
                85                  90                  95

Asn Thr Ile Tyr Leu Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Asn Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp
        115                 120                 125

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro
    130                 135                 140

Ala Gly Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser
145                 150                 155                 160

Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr
                165                 170                 175

Ile Leu Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln
            180                 185                 190

Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val
        195                 200                 205

Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr
    210                 215                 220

Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln
225                 230                 235                 240

Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
                245                 250                 255

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
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            260                 265                 270

Thr Lys Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
        275                 280                 285

Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
    290                 295                 300

Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu
305                 310                 315                 320

Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala
                325                 330                 335

Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
            340                 345                 350

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr
        355                 360                 365

Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln
    370                 375                 380

Gly Thr Ser Val Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro
385                 390                 395                 400

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
                405                 410                 415

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
            420                 425                 430

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
        435                 440                 445

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
    450                 455                 460

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
465                 470                 475                 480

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
                485                 490                 495

Glu Glu Glu Glu Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro
            500                 505                 510

Trp Leu Lys Lys Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe
        515                 520                 525

Phe Ser Gln Leu Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu
    530                 535                 540

Ser Ser Pro Phe Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro
545                 550                 555                 560

Glu Ile Ser Pro Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu
                565                 570                 575

Leu Pro Leu Asn Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly
            580                 585                 590

Gln Asp Pro Thr His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp
        595                 600                 605

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    610                 615                 620

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
625                 630                 635                 640

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                645                 650                 655

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            660                 665                 670
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```
Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        675                 680                 685

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg
    690                 695                 700

His Gln Ala Leu Pro Pro Arg Ser Gly
705                 710


<210> SEQ ID NO 66
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly
1               5                   10                  15

Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn
            20                  25                  30

Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val
        35                  40                  45

Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp Ile Val
        115                 120                 125

Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly Lys Arg Ala
    130                 135                 140

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu Gly Ser His
145                 150                 155                 160

Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Thr Leu Leu
                165                 170                 175

Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala Arg Phe Ser
            180                 185                 190

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu
        195                 200                 205

Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg Thr Ile Pro
    210                 215                 220

Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Ser Thr Ser
225                 230                 235                 240

Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Gln Ile
                245                 250                 255

Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val
            260                 265                 270

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Ser Ile
        275                 280                 285

Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp
    290                 295                 300
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Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe Arg Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Gln
                325                 330                 335

Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Leu
            340                 345                 350

Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
        355                 360                 365

Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
    370                 375                 380

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
385                 390                 395                 400

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
                405                 410                 415

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
            420                 425                 430

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
        435                 440                 445

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    450                 455                 460

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
465                 470                 475                 480

Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val
                485                 490                 495

Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser
            500                 505                 510

Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro
        515                 520                 525

Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu
    530                 535                 540

Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn Thr
545                 550                 555                 560

Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His
                565                 570                 575

Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
            580                 585                 590

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
        595                 600                 605

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
    610                 615                 620

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
625                 630                 635                 640

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
                645                 650                 655

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
            660                 665                 670

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu Pro
        675                 680                 685

Pro Arg Ser Gly
    690
```

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<210> SEQ ID NO 67
<211> LENGTH: 714
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Ile Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser His Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly
115 120 125

His Arg Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Pro Ala Gly Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
145 150 155 160

Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
165 170 175

Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
180 185 190

Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser
195 200 205

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
210 215 220

Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn
225 230 235 240

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly
245 250 255

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
260 265 270

Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser
275 280 285

Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp
290 295 300

Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp
305 310 315 320

Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu
325 330 335

Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe
340 345 350

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Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys
        355                 360                 365

Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly
    370                 375                 380

Gln Gly Thr Ser Val Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala
385                 390                 395                 400

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
                405                 410                 415

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
            420                 425                 430

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
        435                 440                 445

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
    450                 455                 460

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
465                 470                 475                 480

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
                485                 490                 495

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly
            500                 505                 510

Pro Trp Leu Lys Lys Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys
        515                 520                 525

Phe Phe Ser Gln Leu Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp
    530                 535                 540

Leu Ser Ser Pro Phe Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala
545                 550                 555                 560

Pro Glu Ile Ser Pro Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln
                565                 570                 575

Leu Leu Pro Leu Asn Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln
            580                 585                 590

Gly Gln Asp Pro Thr His Leu Val Arg Val Lys Phe Ser Arg Ser Ala
        595                 600                 605

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    610                 615                 620

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
625                 630                 635                 640

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                645                 650                 655

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            660                 665                 670

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        675                 680                 685

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr
    690                 695                 700

Arg His Gln Ala Leu Pro Pro Arg Ser Gly
705                 710


<210> SEQ ID NO 68
<211> LENGTH: 693
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 68

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp
        115                 120                 125

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
    130                 135                 140

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
145                 150                 155                 160

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
                165                 170                 175

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180                 185                 190

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
        195                 200                 205

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
    210                 215                 220

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly Ser
225                 230                 235                 240

Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys Leu
                245                 250                 255

Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val
            260                 265                 270

Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp
        275                 280                 285

Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp
    290                 295                 300

Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr
305                 310                 315                 320

Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser
                325                 330                 335

Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr
            340                 345                 350

Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
        355                 360                 365

Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    370                 375                 380

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
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385 390 395 400

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
405 410 415

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
420 425 430

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
435 440 445

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
450 455 460

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
465 470 475 480

Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys
485 490 495

Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu
500 505 510

Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe
515 520 525

Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro
530 535 540

Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn
545 550 555 560

Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr
565 570 575

His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
580 585 590

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
595 600 605

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
610 615 620

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
625 630 635 640

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
645 650 655

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
660 665 670

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu
675 680 685

Pro Pro Arg Ser Gly
690

<210> SEQ ID NO 69
<211> LENGTH: 713
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 69

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu
20 25 30

Ala Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu

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        35                  40                  45

Ser Val Thr Ile Leu Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln
65                  70                  75                  80

Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Leu Gln Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly
    130                 135                 140

Glu Gly Ser Thr Lys Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
145                 150                 155                 160

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
                165                 170                 175

Tyr Thr Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly
            180                 185                 190

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro
        195                 200                 205

Ala Tyr Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr
    210                 215                 220

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp
225                 230                 235                 240

Thr Ala Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Pro Ala Gly Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln
        275                 280                 285

Pro Gly Gly Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe
    290                 295                 300

Ser Ile Asn Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
305                 310                 315                 320

Ala Phe Val Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp
                325                 330                 335

Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr
            340                 345                 350

Ile Tyr Leu Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr
        355                 360                 365

Tyr Cys Asn Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln
    370                 375                 380

Gly Thr Gln Val Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro
385                 390                 395                 400

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
                405                 410                 415

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
            420                 425                 430

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
        435                 440                 445
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Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
    450                 455                 460

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
465                 470                 475                 480

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
                485                 490                 495

Glu Glu Glu Glu Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro
            500                 505                 510

Trp Leu Lys Lys Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe
        515                 520                 525

Phe Ser Gln Leu Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu
    530                 535                 540

Ser Ser Pro Phe Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro
545                 550                 555                 560

Glu Ile Ser Pro Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu
                565                 570                 575

Leu Pro Leu Asn Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly
            580                 585                 590

Gln Asp Pro Thr His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp
        595                 600                 605

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    610                 615                 620

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
625                 630                 635                 640

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                645                 650                 655

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            660                 665                 670

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        675                 680                 685

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg
    690                 695                 700

His Gln Ala Leu Pro Pro Arg Ser Gly
705                 710


<210> SEQ ID NO 70
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 70

Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1               5                   10                  15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
            20                  25                  30

Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65                  70                  75                  80
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Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
                85                  90                  95

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
        115                 120                 125

Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly
    130                 135                 140

Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
145                 150                 155                 160

Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp
                165                 170                 175

Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp
            180                 185                 190

Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala
        195                 200                 205

Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe
    210                 215                 220

Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225                 230                 235                 240

Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Gln Val
                245                 250                 255

Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly Pro Leu
            260                 265                 270

Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn Arg Met
        275                 280                 285

Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val Ala Ser
    290                 295                 300

Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg
305                 310                 315                 320

Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu Gln Met
                325                 330                 335

Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Ala Val
            340                 345                 350

Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
        355                 360                 365

Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
    370                 375                 380

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
385                 390                 395                 400

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
                405                 410                 415

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
            420                 425                 430

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
        435                 440                 445

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    450                 455                 460

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
465                 470                 475                 480
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Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val
                485                 490                 495

Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser
            500                 505                 510

Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro
        515                 520                 525

Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu
    530                 535                 540

Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn Thr
545                 550                 555                 560

Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His
                565                 570                 575

Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
            580                 585                 590

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
        595                 600                 605

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
    610                 615                 620

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
625                 630                 635                 640

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
                645                 650                 655

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
            660                 665                 670

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu Pro
        675                 680                 685

Pro Arg Ser Gly
    690


<210> SEQ ID NO 71
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 71

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125
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Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Glu Val Gln
                245                 250                 255

Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly Ser Leu Arg
            260                 265                 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His Ala Met Thr
        275                 280                 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile
    290                 295                 300

Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val Lys Gly Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln Met
                325                 330                 335

Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys Ala Lys Asp
            340                 345                 350

Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly Thr Leu Val
        355                 360                 365

Thr Val Ser Ser
    370


<210> SEQ ID NO 72
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 72

Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1               5                   10                  15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
            20                  25                  30

Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65                  70                  75                  80

Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
                85                  90                  95
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Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
115 120 125

Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly
130 135 140

Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
145 150 155 160

Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp
165 170 175

Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp
180 185 190

Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala
195 200 205

Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe
210 215 220

Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225 230 235 240

Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Gln Val
245 250 255

Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly Pro Leu
260 265 270

Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn Arg Met
275 280 285

Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val Ala Ser
290 295 300

Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg
305 310 315 320

Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu Gln Met
325 330 335

Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Ala Val
340 345 350

Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
355 360 365

Val Ser Ser
370

<210> SEQ ID NO 73
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 73

Ser Gly Gly Gly Ser Asp Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> SEQ ID NO 74
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 74

Glu Ala Ala Ala Lys
1 5

<210> SEQ ID NO 75
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75

Gly Gly Gly Gly Ser
1 5

<210> SEQ ID NO 76
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> SEQ ID NO 78
<211> LENGTH: 690
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 78

Gln Val Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly
1 5 10 15

Pro Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn
20 25 30

Arg Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val
35 40 45

Ala Ser Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu
65 70 75 80

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

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```
Ala Val Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp Ile Val
        115                 120                 125

Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly Lys Arg Ala
    130                 135                 140

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu Gly Ser His
145                 150                 155                 160

Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Thr Leu Leu
                165                 170                 175

Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala Arg Phe Ser
            180                 185                 190

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu
        195                 200                 205

Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg Thr Ile Pro
    210                 215                 220

Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Ser Thr Ser
225                 230                 235                 240

Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Gln Ile
                245                 250                 255

Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val
            260                 265                 270

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Ser Ile
        275                 280                 285

Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe Arg Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Gln
                325                 330                 335

Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Leu
            340                 345                 350

Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
        355                 360                 365

Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
    370                 375                 380

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
385                 390                 395                 400

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
                405                 410                 415

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
            420                 425                 430

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
        435                 440                 445

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    450                 455                 460

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
465                 470                 475                 480

Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val
                485                 490                 495
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Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser
            500                 505                 510

Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro
        515                 520                 525

Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu
    530                 535                 540

Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn Thr
545                 550                 555                 560

Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His
                565                 570                 575

Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
            580                 585                 590

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
        595                 600                 605

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
    610                 615                 620

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
625                 630                 635                 640

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
                645                 650                 655

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
            660                 665                 670

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu Pro
        675                 680                 685

Pro Arg
    690


<210> SEQ ID NO 79
<211> LENGTH: 691
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Asp Tyr Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Glu Asp Gly Gly Ser Leu Leu Gly His Arg Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Asp
        115                 120                 125

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
    130                 135                 140
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Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
145                 150                 155                 160

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
                165                 170                 175

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180                 185                 190

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
        195                 200                 205

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
    210                 215                 220

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly Ser
225                 230                 235                 240

Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys Leu
                245                 250                 255

Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val
            260                 265                 270

Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp
        275                 280                 285

Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp
    290                 295                 300

Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr
305                 310                 315                 320

Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser
                325                 330                 335

Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr
            340                 345                 350

Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
        355                 360                 365

Thr Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    370                 375                 380

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
385                 390                 395                 400

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
                405                 410                 415

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
            420                 425                 430

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
        435                 440                 445

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    450                 455                 460

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
465                 470                 475                 480

Gly Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys
                485                 490                 495

Val Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu
            500                 505                 510

Ser Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe
        515                 520                 525

Pro Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro
    530                 535                 540

Leu Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn
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545                 550                 555                 560

Thr Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr
                565                 570                 575

His Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
            580                 585                 590

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
        595                 600                 605

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
    610                 615                 620

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
625                 630                 635                 640

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
                645                 650                 655

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
            660                 665                 670

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu
        675                 680                 685

Pro Pro Arg
    690


<210> SEQ ID NO 80
<211> LENGTH: 690
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80

Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1               5                   10                  15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
            20                  25                  30

Gly Ser His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65                  70                  75                  80

Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
                85                  90                  95

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
        115                 120                 125

Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly
    130                 135                 140

Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
145                 150                 155                 160

Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp
                165                 170                 175

Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp
            180                 185                 190

Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala
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        195                 200                 205

Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe
    210                 215                 220

Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225                 230                 235                 240

Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Pro Ala Gly Gln Val
                245                 250                 255

Lys Leu Glu Glu Ser Gly Gly Glu Leu Val Gln Pro Gly Gly Pro Leu
            260                 265                 270

Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Phe Ser Ile Asn Arg Met
        275                 280                 285

Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Ala Phe Val Ala Ser
    290                 295                 300

Ile Thr Val Arg Gly Ile Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg
305                 310                 315                 320

Phe Thr Ile Ser Val Asp Lys Ser Lys Asn Thr Ile Tyr Leu Gln Met
                325                 330                 335

Asn Ala Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn Ala Val
            340                 345                 350

Ser Ser Asn Arg Asp Pro Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
        355                 360                 365

Val Ser Ser Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
    370                 375                 380

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
385                 390                 395                 400

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
                405                 410                 415

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
            420                 425                 430

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
        435                 440                 445

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    450                 455                 460

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
465                 470                 475                 480

Gly Cys Glu Leu Asn Cys Arg Asn Thr Gly Pro Trp Leu Lys Lys Val
                485                 490                 495

Leu Lys Cys Asn Thr Pro Asp Pro Ser Lys Phe Phe Ser Gln Leu Ser
            500                 505                 510

Ser Glu His Gly Gly Asp Val Gln Lys Trp Leu Ser Ser Pro Phe Pro
        515                 520                 525

Ser Ser Ser Phe Ser Pro Gly Gly Leu Ala Pro Glu Ile Ser Pro Leu
    530                 535                 540

Glu Val Leu Glu Arg Asp Lys Val Thr Gln Leu Leu Pro Leu Asn Thr
545                 550                 555                 560

Asp Ala Tyr Leu Ser Leu Gln Glu Leu Gln Gly Gln Asp Pro Thr His
                565                 570                 575

Leu Val Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
            580                 585                 590

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
        595                 600                 605
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Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
610 615 620

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
625 630 635 640

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
645 650 655

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
660 665 670

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Tyr Arg His Gln Ala Leu Pro
675 680 685

Pro Arg
690

<210> SEQ ID NO 81
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81

gaaatataca agttatatct tgg 23

<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

gaaauauaca aguuauaucu 20

<210> SEQ ID NO 83
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 83

gaaauauaca aguuauaucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 84
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 84

tttcagctct gcatcgtttt gg 22

<210> SEQ ID NO 85
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 85

uuucagcucu gcaucguuu 19

<210> SEQ ID NO 86
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 86

guuucagcuc ugcaucguuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 87
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 87

ttcagctctg catcgttttg gg 22

<210> SEQ ID NO 88
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 88

uucagcucug caucguuuu 19

<210> SEQ ID NO 89
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 89

guucagcucu gcaucguuuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 90
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 90

gcatcgtttt gggttctctt gg 22

<210> SEQ ID NO 91
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 91

gcaucguuuu ggguucucu 19

<210> SEQ ID NO 92
<211> LENGTH: 99
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 92

gcaucguuuu ggguucucug uuuuagagcu agaaauagca aguuaaaaua aggcuagucc 60

guuaucaacu ugaaaaagug gcaccgaguc ggugcuuuu 99

<210> SEQ ID NO 93
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 93

tctcttggct gttactgcca gg 22

<210> SEQ ID NO 94
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94

ucucuuggcu guuacugcc 19

<210> SEQ ID NO 95
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95

gucucuuggc uguuacugcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 96
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96

ttcttttaca tatgggtcct gg 22

<210> SEQ ID NO 97
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 97

uucuuuuaca uaugggucc 19

<210> SEQ ID NO 98
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 98

guucuuuuac auaugggucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 99
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 99

ttctgcttct tttacatatg gg 22

<210> SEQ ID NO 100
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 100

uucugcuucu uuuacauau 19

<210> SEQ ID NO 101
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

guucugcuuc uuuuacauau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> SEQ ID NO 102
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 102

tttctgcttc ttttacatat gg 22

<210> SEQ ID NO 103
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 103

uuucugcuuc uuuuacaua 19

<210> SEQ ID NO 104
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104

guuucugcuu cuuuuacaua guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

1. A bi-specific chimeric antigen receptor (CAR) polypeptide, comprising:

a) a first antigen binding moiety,

b) a second antigen binding moiety,

c) a co-stimulatory signaling domain, and

d) a cytoplasmic signaling domain,

wherein the first antigen binding moiety is a single domain antibody variable fragment (VHH) and the second antigen binding moiety is a single chain variable fragment (scFv), and

wherein the first antigen binding moiety binds a first tumor-associated antigen, and the second antigen binding moiety binds a second tumor-associated antigen, which optionally is different from the first tumor associated antigen.

2. The bi-specific CAR polypeptide of claim 1, wherein the first and second tumor antigens are selected from the group consisting of 5T4, CD2, CD3, CD5, CD7, CD19, CD20, CD22, CD30, CD33, CD38, CD70, CD123, CD133, CD171, CEA, CS1, BCMA, BAFF-R, PSMA, PSCA, desmoglein (Dsg3), HER-2, FAP, FSHR, NKG2D, GD2, EGFRVIII, mesothelin, ROR1, MAGE, MUC1, MUC16, GPC3, Lewis Y, Claudin 18.2, and VEGFRII.

3. The bi-specific CAR polypeptide of claim 1, wherein the first tumor antigen is CD19 and the second tumor antigen is BCMA, or vice versa.

4. The bi-specific CAR polypeptide of claim 3, wherein the first antigen binding moiety is a VHH fragment binding to CD19 (anti-CD19 VHH) and the second antigen binding moiety is a scFv binding to BCMA (anti-BCMA scFv); or wherein the first antigen binding moiety is a VHH binding to BCMA (anti-BCMA VHH) and the second antigen binding moiety is a scFv fragmenting binding to CD19 (anti-CD19 scFv).

5. The bi-specific CAR polypeptide of claim 4, wherein the anti-CD19 scFv comprises the amino acid sequence of SEQ ID. NO: 7, 8, or 9; and/or wherein the anti-BCMA VHH comprises the amino acid sequence of SEQ ID NO: 4, 5, or 6.

6. The bi-specific CAR polypeptide of claim 5, wherein a) and b) comprises the amino acid sequence of SEQ ID NO:11, 44, 63, 64, 67, 68, 71, or 79, optionally SEQ ID NO: 11.

7. The bi-specific CAR polypeptide of claim 4, wherein the anti-CD19 VHH comprises the amino acid sequence of SEQ ID NO: 1, 2, or 3; and/or wherein the anti-BCMA scFv comprises the amino acid sequence of SEQ ID NO: 10.

8. The bi-specific CAR polypeptide of claim 7, wherein a) and b) comprises the amino acid sequence of SEQ ID NO: 12, 65, 66, 69, 70, 72, 78, or 80, optionally SEQ ID NO: 12.

9. A bi-specific chimeric antigen receptor (CAR) polypeptide, comprising:

a) a first antigen binding moiety, which is a truncated fragment of APRIL that binds to BCMA;

b) a second antigen binding moiety, which is a single domain antibody variable fragment (VHH) or a single chain variable fragment (scFv) that binds a tumor associated antigen,

c) a co-stimulatory signaling domain, and

d) a cytoplasmic signaling domain,

10. The bi-specific CAR polypeptide of claim 9, wherein the truncated fragment of APRIL that binds BCMA comprises an amino acid sequence at least 90% identical to SEQ ID NO: 58; optionally wherein the truncated fragment of APRIL comprises the amino acid sequence of SEQ ID NO: 58.

11. The bi-specific CAR polypeptide of claim 9, wherein the second antigen-binding moiety is an anti-CD19 scFv or an anti-CD19 VHH.

12. The bi-specific CAR polypeptide of claim 11, wherein the anti-CD19 scFv comprises the amino acid sequence of SEQ ID NO: 7, 8, or 9; or wherein the anti-CD19 VHH comprises the amino acid sequence of SEQ ID NO: 1, 2, or 3.

13. The bi-specific CAR polypeptide of claim 12, wherein a) and b) comprise the amino acid sequence of SEQ ID NO: 59, 60, 61, or 62.

14. The bi-specific CAR polypeptide of claim 1, further comprising a peptide linker between the first antigen binding moiety and the second antigen binding moiety, optionally wherein the peptide linker is about 4-40 amino acids in length.

15. The bi-specific CAR polypeptide of claim 1, wherein the co-stimulatory signaling domain is from 4-1BB or CD28.

16. The bi-specific CAR polypeptide of claim 1, wherein the cytoplasmic signaling domain comprises a CD3 z cyto-

plasmic signaling domain, an IL-2Rβ cytoplasmic signaling domain, or a combination thereof.

17. The bi-specific CAR polypeptide of claim **16**, wherein the cytoplasmic signaling domain comprises the CD3 z cytoplasmic signaling domain, which optionally comprises a STAT binding motif.

18. The bi-specific CAR polypeptide of claim **1**, further comprising a transmembrane domain, a hinge domain, or a combination thereof, which optionally is located between the first or second antigen binding moiety and the co-stimulatory domain.

19. The bi-specific CAR polypeptide of claim **18**, wherein the transmembrane domain and/or the hinge domain is from CD8.

20. The bi-specific CAR polypeptide of claim **1**, which comprises the amino acid sequence of any one of SEQ ID NOs: 63-70.

21. A population of genetically engineered immune cells, which expressing a bi-specific CAR polypeptide of claim **1**.

22. The population of genetically engineered immune cells of claim **21**, which further comprise one or more of the following features:

e) have one or more disrupted endogenous genes encoding one or more proinflammatory cytokines; and

f) express one or more antagonists targeting the proinflammatory cytokines.

23. The population of genetically engineered immune cells of claim **22**, wherein the proinflammatory cytokines are selected from the group consisting of interferon gamma (IFNγ), interleukin 6 (IL-6), GM-CSF, and interleukin 1 (IL-1).

24. The population of genetically engineered immune cells of claim **22**, wherein the genetically engineered immune cells comprise a disrupted endogenous interferon gamma gene, a disrupted endogenous GM-CSF gene, or a combination thereof.

25. The population of genetically engineered immune cells of claim **24**, wherein the endogenous interferon gamma gene, the endogenous GM-CSF gene, or both are disrupted by a CRISPR/Cas gene editing system.

26. The population of genetically engineered immune cells of claim **22**, wherein the genetically engineered immune cells express an IL-6 antagonist, an IFNγ antagonist, an IL-1 antagonist, or a combination thereof.

27. The population of genetically engineered immune cells of claim **26**, wherein the IL-6 antagonist is an antibody specific to human IL6 (anti-IL6 antibody) or an antibody specific to human IL6R (anti-IL6R antibody), and/or wherein the IFNγ antagonist is an antibody specific to human IFNγ (anti-IFNγ antibody).

28. The population of genetically engineered immune cells of claim **27**, wherein the anti-IL6 antibody, the anti-IFNγ antibody, or both are scFv antibodies.

29. The population of genetically engineered immune cells of claim **28**, wherein the genetically engineered immune cells express an anti-IFNγ scFv comprising:

(i) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 13, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 14;

(ii) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 16, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 17; or

(iii) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 19, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 20.

30. The population of genetically engineered immune cells of claim **29**, wherein the anti-IFNγ scFv comprises the amino acid sequence of SEQ. ID. NO: 15, 18, or 21.

31. The population of genetically engineered immune cells of claim **30**, wherein the genetically engineered immune cells express a bi-specific CAR comprising the amino acid sequence of any one of SEQ ID NOs: 44, 63-70 or 78-80.

32. The population of genetically engineered immune cells of claim **28**, wherein the genetically engineered immune cells express an anti-IL6 scFv comprising:

(a) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 24, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 25;

(b) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 26, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 27; or

(c) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 30, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 31.

33. The population of genetically engineered immune cells of claim **28**, wherein the genetically engineered immune cells express an anti-IL6R scFv comprising:

(a) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 22, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 23;

(b) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 28, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 29; or

(c) a heavy chain variable region, which comprises the amino acid sequence of SEQ ID NO: 32, and a light chain variable region, which comprises the amino acid sequence of SEQ ID NO: 33.

34. The population of genetically engineered immune cells of claim **32**, wherein the anti-IL6 scFv or anti-IL6R scFv comprises the amino acid sequence of SEQ ID NO: 34, 35, 36, or 37.

35. The population of genetically engineered immune cells of claim **22**, wherein genetically engineered immune cells express an IL-1 antagonist, and wherein the IL-1 antagonist is IL-1RA, which comprises the amino acid sequence of SEQ ID NO: 54.

36. The population of genetically engineered immune cells of claim **22**, wherein the genetically engineered immune cells comprise T cells, tumor infiltrating lymphocytes, Natural Killer (NK) cells, dendritic cells, macrographs, B cells, neutrophils, eosinophils, basophils, mast cells, myeloid-derived suppressor cells, mesenchymal stem cells, precursors thereof, or a combination thereof.

37. The population of genetically engineered immune cells of claim **22**, wherein the immune cells are human immune cells.

38. The population of genetically engineered immune cells of claim **37**, which comprise human T cells.

39. A pharmaceutical composition, comprising a population of immune cells of claim **22** and a pharmaceutically acceptable carrier.

40. A method for reducing or eliminating undesired cells in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of the population of immune cells of claim **22** or a pharmaceutical composition comprising the population of immune cells of claim **39**.

41. The method of claim **40**, wherein the subject is a human patient having a cancer, which comprises cancer cells expressing the first tumor associated antigen, the second tumor associated antigen, or both.

42. The method of claim **40**, wherein the subject is a human patient having a solid tumor or a hematological cancer.

43. The method of claim **42**, wherein the human patient has a solid tumor, which is selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, liver cancer, glioblastoma (GBM), prostate cancer, ovarian cancer, mesothelioma, colon cancer, and stomach cancer.

44. The method of claim **42**, wherein the human patient has a hematological cancer, which is leukemia, lymphoma, or multiple myeloma.

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