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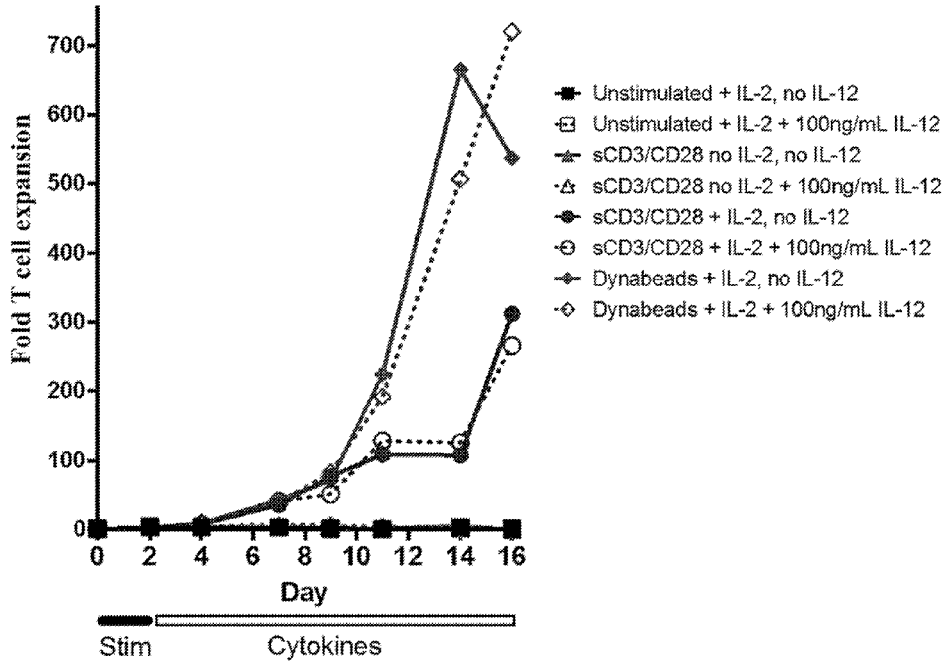
(54) Title: CD19 COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

Figure 28A



(57) Abstract: The present invention provides biocircuit systems, effector modules and compositions for cancer immunotherapy. Methods for inducing anti-cancer immune responses in a subject are also provided.

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[Continued on next page]

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CD19 COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the US Provisional Patent Application No. 62/466,601, filed on March 3, 2017 entitled Compositions and Methods for Immunotherapy and the US Provisional Patent Application No. 62/484,052, filed on April 11, 2017 entitled Anti CD19 compositions and methods for immunotherapy, the contents of each of which are herein incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 2095_1201PCT_SL.txt, created on March 2, 2018, which is 2,116,001 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions and methods for immunotherapy. Provided in the present invention include polypeptides of biocircuit systems, effector modules, stimulus response elements (SREs) and immunotherapeutic agents, polynucleotides encoding the same, vectors and cells containing the polypeptides and/or polynucleotides for use in cancer immunotherapy. In one embodiment, the compositions comprise destabilizing domains (DDs) which tune protein stability.

BACKGROUND OF THE INVENTION

[0004] Cancer immunotherapy aims to eradicate cancer cells by rejuvenating the tumoricidal functions of tumor-reactive immune cells, predominantly T cells. Strategies of cancer immunotherapy including the recent development of checkpoint blockade, adoptive cell transfer (ACT) and cancer vaccines which can increase the anti-tumor immune effector cells have produced remarkable results in several tumors.

[0005] The impact of host anti-tumor immunity and cancer immunotherapy is impeded by three major hurdles: 1) low number of tumor antigen-specific T cells due to clonal deletion; 2) poor activation of innate immune cells and accumulation of tolerogenic antigen-presenting cells in the tumor microenvironment; and 3) formation of an immunosuppressive tumor microenvironment. Particularly, in solid tumors the therapeutic efficacy of immunotherapeutic regimens remains unsatisfactory due to lack of an effective an anti-tumor response in the immunosuppressive tumor microenvironment. Tumor cells often induce immune tolerance or suppression and such tolerance is acquired because even truly foreign tumor antigens will

become tolerated. Such tolerance is also active and dominant because cancer vaccines and adoptive transfer of pre-activated immune effector cells (e.g., T cells), are subject to suppression by inhibitory factors in the tumor microenvironment (TME).

[0006] In addition, administration of engineered T cells could result in on/off target toxicities as well as a cytokine release syndrome (reviewed by Tey *Clin. Transl. Immunol.*, 2014, 3: e17 10.1038).

[0007] Development of a tunable switch that can turn on or off the transgenic immunotherapeutic agent expression is needed in case of adverse events. For example, adoptive cell therapies may have a very long and an indefinite half-life. Since toxicity can be progressive, a safety switch is desired to eliminate the infused cells. Systems and methods that can tune the transgenic protein level and expression window with high flexibility can enhance therapeutic benefit, and reduce potential side effects.

[0008] To develop regulatable therapeutic agents for disease therapy, in particular cancer immunotherapy, the present invention provides biocircuit systems to control the expression of immunotherapeutic agents. The biocircuit system comprises a stimulus and at least one effector module that responds to the stimulus. The effector module may include a stimulus response element (SRE) that binds and is responsive to a stimulus and an immunotherapeutic agent operably linked to the SRE. In one example, a SRE is a destabilizing domain (DD) which is destabilized in the absence of its specific ligand and can be stabilized by binding to its specific ligand.

SUMMARY OF THE INVENTION

[0009] The present invention provides compositions and methods for immunotherapy. The compositions relate to tunable systems and agents that induce anti-cancer immune responses in a cell or in a subject. The tunable system and agent may be a biocircuit system comprising at least one effector module that is responsive to at least one stimulus. The biocircuit system may be, but is not limited to, a destabilizing domain (DD) biocircuit system, a dimerization biocircuit system, a receptor biocircuit system, and a cell biocircuit system. These systems are further taught in co-owned U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016, 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety).

[0010] In some embodiments, the composition for inducing an immune response may comprise an effector module. In some embodiments, the effector module may comprise a stimulus response element (SRE) operably linked to at least one payload. In one aspect, the payload may be an immunotherapeutic agent.

[0011] In some embodiments, the immunotherapeutic agent may be selected from, but is not limited to a chimeric antigen receptor (CAR) and an antibody.

[0012] In one aspect, the SRE of the composition may be responsive to or interact with at least one stimulus.

[0013] In some embodiments, the SRE may comprise a destabilizing domain (DD). The DD may be derived from a parent protein or from a mutant protein having one, two, there, or more amino acid mutations compared to the parent protein. In some embodiments, the parent protein may be selected from, but is not limited to, human protein FKBP, comprising the amino acid sequence of SEQ ID NO. 3; human DHFR (hDHFR), comprising the amino acid sequence of SEQ ID NO. 2; E. Coli DHFR, comprising the amino acid sequence of SEQ ID NO. 1; PDE5, comprising the amino acid sequence of SEQ ID NO. 4; PPAR, gamma comprising the amino acid sequence of SEQ ID NO. 5; CA2, comprising the amino acid sequence of SEQ ID NO. 6; or NQO2, comprising the amino acid sequence of SEQ ID NO. 7.

[0014] In one aspect, the parent protein is hDHFR and the DD comprises a mutant protein. The mutant protein may comprise a single mutation and may be selected from, but not limited to hDHFR (I17V), hDHFR (F59S), hDHFR (N65D), hDHFR (K81R), hDHFR (A107V), hDHFR (Y122I), hDHFR (N127Y), hDHFR (M140I), hDHFR (K185E), hDHFR (N186D), and hDHFR (M140I), hDHFR (Amino acid 2-187 of WT; N127Y), hDHFR (Amino acid 2-187 of WT; I17V), hDHFR (Amino acid 2-187 of WT; Y122I), and hDHFR (Amino acid 2-187 of WT; K185E). In some embodiments, the mutant protein may comprise two mutations and may be selected from, but not limited to, hDHFR (C7R, Y163C), hDHFR (A10V, H88Y), hDHFR (Q36K, Y122I), hDHFR (M53T, R138I), hDHFR (T57A, I72A), hDHFR (E63G, I176F), hDHFR (G21T, Y122I), hDHFR (L74N, Y122I), hDHFR (V75F, Y122I), hDHFR (L94A, T147A), DHFR (V121A, Y22I), hDHFR (Y122I, A125F), hDHFR (H131R, E144G), hDHFR (T137R, F143L), hDHFR (Y178H, E18IG), and hDHFR (Y183H, K185E), hDHFR (E162G, I176F) hDHFR (Amino acid 2-187 of WT; I17V, Y122I), hDHFR (Amino acid 2-187 of WT; Y122I, M140I), hDHFR (Amino acid 2-187 of WT; N127Y, Y122I), hDHFR (Amino acid 2-187 of WT; E162G, I176F), and hDHFR (Amino acid 2-187 of WT; H131R, E144G), and hDHFR (Amino acid 2-187 of WT; Y122I, A125F). In some embodiments, the mutant may comprise three mutations and the mutant may be selected from hDHFR (V9A, S93R, P150L), hDHFR (I8V, K133E, Y163C), hDHFR (L23S, V121A, Y157C), hDHFR (K19E, F89L, E181G), hDHFR (Q36F, N65F, Y122I), hDHFR (G54R, M140V, S168C), hDHFR (V110A, V136M, K177R), hDHFR (Q36F, Y122I, A125F), hDHFR (N49D, F59S, D153G), and hDHFR (G21E, I72V, I176T), hDHFR (Amino acid 2-187 of WT; Q36F, Y122I, A125F), hDHFR (Amino acid

2-187 of WT; Y122I, H131R, E144G), hDHFR (Amino acid 2-187 of WT; E31D, F32M, V116I), and hDHFR (Amino acid 2-187 of WT; Q36F, N65F, Y122I). In some embodiments, the mutant may comprise four or more mutations and the mutant may be selected from hDHFR (V2A, R33G, Q36R, L100P, K185R), hDHFR (Amino acid 2-187 of WT; D22S, F32M, R33S, Q36S, N65S), hDHFR (I17N, L98S, K99R, M112T, E151G, E162G, E172G), hDHFR (G16S, I17V, F89L, D96G, K123E, M140V, D146G, K156R), hDHFR (K81R, K99R, L100P, E102G, N108D, K123R, H128R, D142G, F180L, K185E), hDHFR (R138G, D142G, F143S, K156R, K158E, E162G, V166A, K177E, Y178C, K185E, N186S), hDHFR (N14S, P24S, F35L, M53T, K56E, R92G, S93G, N127S, H128Y, F135L, F143S, L159P, L160P, E173A, F180L), hDHFR (F35L, R37G, N65A, L68S, K69E, R71G, L80P, K99G, G117D, L132P, I139V, M140I, D142G, D146G, E173G, D187G), hDHFR (L28P, N30H, M38V, V44A, L68S, N73G, R78G, A97T, K99R, A107T, K109R, D111N, L134P, F135V, T147A, I152V, K158R, E172G, V182A, E184R), hDHFR (V2A, I17V, N30D, E31G, Q36R, F59S, K69E, I72T, H88Y, F89L, N108D, K109E, V110A, I115V, Y122D, L132P, F135S, M140V, E144G, T147A, Y157C, V170A, K174R, N186S), hDHFR (L100P, E102G, Q103R, P104S, E105G, N108D, V113A, W114R, Y122C, M126I, N127R, H128Y, L132P, F135P, I139T, F148S, F149L, I152V, D153A, D169G, V170A, I176A, K177R, V182A, K185R, N186S), and hDHFR (A10T, Q13R, N14S, N20D, P24S, N30S, M38T, T40A, K47R, N49S, K56R, I61T, K64R, K69R, I72A, R78G, E82G, F89L, D96G, N108D, M112V, W114R, Y122D, K123E, I139V, Q141R, D142G, F148L, E151G, E155G, Y157R, Q171R, Y183C, E184G, K185del, D187N).

[0015] In one aspect, the stimulus of the SRE may be Trimethoprim or Methotrexate.

[0016] In some embodiments, the immunotherapeutic agent of the effector module is a chimeric antigen receptor (CAR). The chimeric antigen may comprise an extracellular target moiety; a transmembrane domain; an intracellular signaling domain; and optionally, one or more co-stimulatory domains.

[0017] In one aspect, the CAR may be selected from, but is not limited to a standard CAR, a split CAR, an off-switch CAR, an on-switch CAR, a first-generation CAR, a second-generation CAR, a third-generation CAR, or a fourth-generation CAR.

[0018] In some embodiments, the extracellular target moiety of the CAR may be selected from, but is not limited to an Ig NAR, a Fab fragment, a Fab' fragment, a F(ab)'2 fragment, a F(ab)'3 fragment, an Fv, a single chain variable fragment (scFv), a bis-scFv, a (scFv)2, a minibody, a diabody, a triabody, a tetrabody, an intrabody, a disulfide stabilized Fv protein (dsFv), a unibody, a nanobody, and an antigen binding region derived from an antibody that may

specifically bind to any of a protein of interest, a ligand, a receptor, a receptor fragment or a peptide aptamer.

[0019] In one aspect, the extracellular target moiety may be an scFv derived from an antibody. In one aspect, the scFv may specifically bind to a CD19 antigen

[0020] In one aspect, the scFv of the CAR may be a CD19 scFv. In some embodiments, the CD19 scFv may comprise a heavy chain variable region having an amino acid sequence independently selected from the group consisting of SEQ ID NO: 49-80, and a light chain variable region having an amino acid sequence independently selected from the group consisting of any of SEQ ID NOs: 81-122. In some embodiments, the CD19 scFv may comprise an amino acid sequence selected from the group consisting of any of SEQ ID NOs: 123-267 and 624.

[0021] In some embodiments, the intracellular signaling domain of the CAR may be a signaling domain derived from T cell receptor CD3zeta. In some embodiments, the intracellular signaling domain may be selected from a cell surface molecule selected from the group consisting of FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. In one aspect, the CAR may include a co-stimulatory domain. In some embodiments, the co-stimulatory domain may be selected from the group consisting of 2B4, HVEM, ICOS, LAG3, DAP10, DAP12, CD27, CD28, 4-1BB (CD137), OX40 (CD134), CD30, CD40, ICOS (CD278), glucocorticoid-induced tumor necrosis factor receptor (GITR), lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, and B7-H3.

[0022] (b) the co-stimulatory domain is present and is selected from the group consisting of 2B4, HVEM, ICOS, LAG3, DAP10, DAP12, CD27, CD28, 4-1BB (CD137), OX40 (CD134), CD30, CD40, ICOS (CD278), glucocorticoid-induced tumor necrosis factor receptor (GITR), lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, and B7-H3.

[0023] In some embodiments, the intracellular signaling domain of the CAR may be a T cell receptor CD3zeta signaling domain, which may comprise the amino acid sequence of SEQ ID NO: 339.

[0024] In some embodiments, T cell receptor CD3zeta signaling domain of the CAR, comprising the amino acid sequence of SEQ ID NO: 626 may further comprise at least one co-stimulatory domain. The co-stimulatory domain may comprise an amino acid sequence of SEQ ID NOs: 268-374.

[0025] In one embodiment, the transmembrane domain of the CAR may be derived from a transmembrane region of an alpha, beta or zeta chain of a T-cell receptor. In one aspect, the transmembrane domain may be derived from the CD3 epsilon chain of a T-cell receptor. In one embodiment, the transmembrane domain may be derived from a molecule selected from CD4,

CD5, CD8, CD8α, CD9, CD16, CD22, CD33, CD28, CD37, CD45, CD64, CD80, CD86, CD148, DAP 10, EpoRI, GITR, LAG3, ICOS, Her2, OX40 (CD134), 4-1BB (CD137), CD152, CD154, PD-1, or CTLA-4. In another embodiment, the transmembrane domain may be derived from an immunoglobulin selected from IgG1, IgD, IgG4, and an IgG4 Fc region. In one aspect, the transmembrane domain may comprise an amino acid sequence selected from the group consisting of any of SEQ ID NOs: 375-425 and 897-907.

[0026] In some embodiments, the CAR of the effector module may further comprise a hinge region near the transmembrane domain. In one aspect, the hinge region may comprise an amino acid sequence selected from the group consisting of any of SEQ ID NOs: 426-504.

[0027] In some embodiments, the immunotherapeutic agent may be an antibody that is specifically immunoreactive to an antigen selected from a tumor specific antigen (TSA), a tumor associated antigen (TAA), or an antigenic epitope.

[0028] In one aspect, the antigen may be an antigenic epitope. In some embodiments, the antigenic epitope may be CD19.

[0029] In some embodiments, the antibody may comprise a heavy chain variable region having an amino acid sequence independently selected from the group consisting of any of SEQ ID NOs: 49-80 and a light chain variable region having an amino acid sequence independently selected from the group consisting of any of SEQ ID NOs: 81-122. In one aspect, the antibody may comprise an amino acid sequence selected from the group consisting of any of SEQ ID NOs: 123-267 and 624.

[0030] In one aspect, the first effector module may comprise the amino acid sequence of any of SEQ ID NO: 635-649, 1005-1010, 1015-1018 and 1215-1231.

[0031] In some embodiments, the first SRE of the effector module may stabilize the immunotherapeutic agent by a stabilization ratio of 1 or more, wherein the stabilization ratio may comprise the ratio of expression, function or level of the immunotherapeutic agent in the presence of the stimulus to the expression, function or level of the immunotherapeutic agent in the absence of the stimulus.

[0032] In some embodiments, the SRE may destabilize the immunotherapeutic agent by a destabilization ratio between 0, and 0.09, wherein the destabilization ratio may comprise the ratio of expression, function or level of the immunotherapeutic agent in the absence of the stimulus specific to the SRE to the expression, function or level of the immunotherapeutic agent that is expressed constitutively, and in the absence of the stimulus specific to the SRE.

[0033] The present invention also provides polynucleotides comprising the compositions of the invention.

[0034] In one aspect, the polynucleotides may be a DNA or RNA molecule. In one aspect, the polynucleotides may comprise spatiotemporally selected codons. In one aspect, the polynucleotides of the invention may be a DNA molecule. In some embodiments, the polynucleotides may be an RNA molecule. In one aspect, the RNA molecule may be a messenger molecule. In some embodiments, the RNA molecule may be chemically modified.

[0035] In some embodiments, the polynucleotides may further comprise, at least one additional feature selected from, but not limited to, a promoter, a linker, a signal peptide, a tag, a cleavage site and a targeting peptide.

[0036] The present invention also provides vectors comprising polynucleotides described herein. In one aspect, the vector may be a viral vector. In some embodiments, the viral vector may be a retroviral vector, a lentiviral vector, a gamma retroviral vector, a recombinant AAV vector, an adeno viral vector, and an oncolytic viral vector.

[0037] The present invention also provides immune cells for adoptive cell transfer (ACT) which may express the compositions of the invention, the polynucleotides described herein. In one aspect, the immune cells may be infected or transfected with the vectors described herein. The immune cells for ACT may be selected from, but not limited to a CD8+ T cell, a CD4+ T cell, a helper T cell, a natural killer (NK) cell, a NKT cell, a cytotoxic T lymphocyte (CTL), a tumor infiltrating lymphocyte (TIL), a memory T cell, a regulatory T (Treg) cell, a cytokine-induced killer (CIK) cell, a dendritic cell, a human embryonic stem cell, a mesenchymal stem cell, a hematopoietic stem cell, or a mixture thereof.

[0038] In some embodiments, the immune cells may be autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

[0039] In some embodiments, the immune cell may further express a composition comprising a second effector module, said second effector module comprising a second SRE linked to a second immunotherapeutic agent. In one aspect, the second immunotherapeutic agent may be selected from a cytokine, and a cytokine- cytokine receptor fusion.

[0040] In one aspect, the second immunotherapeutic agent may be a cytokine. In one aspect, the cytokine may be IL12 or IL15.

[0041] In one aspect, the second immunotherapeutic agent may be a cytokine- cytokine receptor fusion polypeptide.

[0042] In some embodiments, the cytokine-cytokine receptor fusion polypeptide may be selected from, but is not limited to a IL12-IL12 receptor fusion polypeptide, a IL15-IL15 receptor fusion polypeptide, and a IL15-IL15 receptor sushi domain fusion polypeptide.

[0043] The present invention provides methods for reducing a tumor volume or burden in a subject comprising contacting the subject with the immune cells of the invention. Also provided herein, is a method for inducing an anti-tumor immune response in a subject, comprising administering the immune cells of the system to the subject.

[0044] The present invention also provides methods for enhancing the expansion and/or survival of immune cells, comprising contacting the immune cells with the compositions of the invention, the polynucleotides of the invention, and/or the vectors of the invention.

[0045] Also provided herein, is a method for inducing an immune response in a subject, administering the compositions of the invention, the polynucleotides of the invention, and/or the immune cells of the invention to the subject.

[0046] The present invention also provides a method of identifying a domain of a CD19 antigen which will not bind the FMC63 antibody (FMC63-distinct CD19 binding domain). The method may comprise (a) preparing a composition comprising a CD19 antigen, (b) contacting the composition in (a) with saturating levels of FMC63 antibody, (c) contacting the composition of step (b) with one or more selected members of a library of potential CD19 binders; and (d) identifying a binding domain on the CD19 antigen based on the differential binding of the selected members of the library of CD19 binders compared to the binding of FMC63. In some embodiments, the binding domains of the library may be generated using phage display techniques with the CD19 antigen as the seed sequence. In one aspect, the binding domain may be selected from a Fab fragment, a Fab' fragment, a F(ab)'2 fragment, a F(ab)'3 fragment, Fv, a single chain variable fragment (scFv), a bis-scFv, a (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein (dsFv), a unibody, a nanobody, or an antigen binding region of an antibody, and an antibody fragment. In one aspect, the CD19 antigen may be selected from a whole or a portion of a human CD19 antigen, and a whole or a portion of a Rhesus CD19 antigen.

[0047] The present invention also provides chimeric antigen receptors that may comprise the FMC63-distinct CD19 binding domain obtained according to the methods described herein. Also, provided herein is a stimulus response element (SRE) operably linked to the chimeric antigen receptors that include the FMC63-distinct CD19 binding domain.

[0048] In some embodiments, the effector module comprises a stimulus response element (SRE) and at least one payload comprising a protein of interest (POI).

[0049] In some embodiments, the SRE may be a destabilizing domain (DD). In some examples, the DD is a mutant domain derived from a protein such as FKBP (FK506 binding

protein), E. coli DHFR (Dihydrofolate reductase) (ecDHFR), human DHFR (hDHFR), or any protein of interest. In this context, the biocircuit system is a DD biocircuit system.

[0050] The payload may be any immunotherapeutic agent used for cancer immunotherapy such as a chimeric agent receptor (CAR) such as CD19 CAR that targets any molecule of tumor cells, an antibody, an antigen binding domain or combination of antigen binding domains, a cytokine such as IL12, IL15 or IL15/IL15Ra fusion, or any agent that can induce an immune response. The SRE and payload may be operably linked through one or more linkers and the positions of components may vary within the effector module.

[0051] In some embodiments, the effector module may further comprise of one or more additional features such as linker sequences (with specific sequences and lengths), cleavage sites, regulatory elements (that regulate expression of the protein of interest such as microRNA targeting sites), signal sequences that lead the effector module to a specific cellular or subcellular location, penetrating sequences, or tags and biomarkers for tracking the effector module.

[0052] In some embodiments, the DD may stabilize the immunotherapeutic agent with a stabilization ratio of at least one in the presence of the stimulus. According to the present invention, the DD may destabilize the immunotherapeutic agent in the absence of ligand with a destabilization ratio between 0, and 0.99.

[0053] The invention provides isolated biocircuit polypeptides, effector modules, stimulus response elements (SREs) and payloads, as well as polynucleotides encoding any of the foregoing; vectors comprising polynucleotides of the invention; and cells expressing polypeptides, polynucleotides and vectors of the invention. The polypeptides, polynucleotides, viral vectors and cells are useful for inducing anti-tumor immune responses in a subject.

[0054] In some embodiments, the vector of the invention is a viral vector. The viral vector may include, but is not limited to a retroviral vector, an adenoviral vector, an adeno-associated viral vector, or a lentiviral vector.

[0055] In some embodiments, the vector of the invention may be a non-viral vector, such as a nanoparticles and liposomes.

[0056] The present invention also provides immune cells engineered to include one or more polypeptides, polynucleotides, or vectors of the present invention. The cells may be immune effector cells, including T cells such as cytotoxic T cells, helper T cells, memory T cells, regulatory T cells, natural killer (NK) cells, NK T cells, cytokine-induced killer (CIK) cells, cytotoxic T lymphocytes (CTLs), and tumor infiltrating lymphocytes (TILs). The engineered cell may be used for adoptive cell transfer for treating a disease (e.g., a cancer).

[0057] The present invention also provides methods for inducing immune responses in a subject using the compositions of the invention. Also provided are methods for reducing a tumor burden in a subject using the compositions of the invention.

[0058] Also provided herein are methods for identifying FMC63-distinct binding domains and using CD19 antigens in which the FMC63 binding epitope is masked or absent. In some embodiments, the FMC63 binding domain may be included in the payloads and effector modules of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0059] Figure 1 shows an overview diagram of a biocircuit system of the invention. The biocircuit comprises a stimulus and at least one effector module responsive to a stimulus, where the response to the stimulus produces a signal or outcome. The effector module comprises at least one stimulus response element (SRE) and one payload.

[0060] Figure 2 shows representative effector modules carrying one payload. The signal sequence (SS), SRE and payload may be located or positioned in various arrangements without (A to F) or with (G to Z, and AA to DD) a cleavage site. An optional linker may be inserted between each component of the effector module.

[0061] Figure 3 shows representative effector modules carrying two payloads without a cleavage site. The two payloads may be either directly linked to each other or separated.

[0062] Figure 4 shows representative effector modules carrying two payloads with a cleavage site. In one embodiment, an SS is positioned at the N-terminus of the construct, while other components: SRE, two payloads and the cleavage site may be located at different positions (A to L). In another embodiment, the cleavage site is positioned at the N-terminus of the construct (M to X). An optional linker may be inserted between each component of the effector module.

[0063] Figure 5 shows effector modules of the invention carrying two payloads, where an SRE is positioned at the N-terminus of the construct (A to L), while SS, two payloads and the cleavage site can be in any configuration. An optional linker may be inserted between each component of the effector module.

[0064] Figure 6 shows effector modules of the invention carrying two payloads, where either the two payloads (A to F) or one of the two payloads (G to X) is positioned at the N-terminus of the construct (A to L), while SS, SRE and the cleavage site can be in any configuration. An optional linker may be inserted between each component of the effector module.

[0065] Figure 7 depicts representative configurations of the stimulus and effector module within a biocircuit system. A trans-membrane effector module is activated either by a free stimulus (Figure 7A) or a membrane bound stimulus (Figure 7B) which binds to SRE. The

response to the stimulus causes the cleavage of the intracellular signal/payload, which activates down-stream effector/payload.

[0066] Figure 8 depicts a dual stimulus-dual presenter biocircuit system, where two bound stimuli (A and B) from two different presenters (e.g., different cells) bind to two different effector modules in a single receiver (e.g., another single cell) simultaneously and create a dual-signal to downstream payloads.

[0067] Figure 9 depicts a dual stimulus-single presenter biocircuit system, where two bound stimuli (A and B) from the same presenter (e.g., a single cell) bind to two different effector modules in another single cell simultaneously and create a dual-signal.

[0068] Figure 10 depicts a single-stimulus-bridged receiver biocircuit system. In this configuration, a bound stimulus (A) binds to an effector module in the bridge cell and creates a signal to activate a payload which is a stimulus (B) for another effector module in the final receiver (e.g., another cell).

[0069] Figure 11 depicts a single stimulus-single receiver biocircuit system, wherein the single receiver contains the two effector modules which are sequentially activated by a single stimulus.

[0070] Figure 12 depicts a biocircuit system which requires a dual activation. In this embodiment, one stimulus must bind the transmembrane effector module first to prime the receiver cell being activated by the other stimulus. The receiver only activates when it senses both stimuli (B).

[0071] Figure 13 depicts a standard effector module of a chimeric antigen receptor (CAR) system which comprises an antigen binding domain as an SRE, and signaling domain(s) as payload.

[0072] Figure 14 depicts the structure design of a regulatable CAR system, where the trans-membrane effector modules comprise antigen binding domains sensing an antigen and a first switch domain and the intracellular module comprises a second switch domain and signaling domains. A stimulus (e.g., a dimerization small molecule) can dimerize the first and second switch domains and assemble an activated CAR system.

[0073] Figure 15 shows schematic representation of CAR systems having one (A) or two (B and C) SREs incorporated into the effector module.

[0074] Figure 16 depicts a split CAR design to control T cell activation by a dual stimulus (e.g., an antigen and small molecule). Figure 16A shows normal T cell activation which entails a dual activation of TCR and co-stimulatory receptor. The regular CAR design (Figure 16B) combines the antigen recognition domain with TCR signaling motif and co-stimulatory motif in a single molecule. The split CAR system separates the components of the regular CAR into two

separate effector modules which can be reassembled when a heterodimerizing small molecule (stimulus) is present.

[0075] Figure 17 depicts the positive and negative regulation of CAR engineered T cell activation. The absence or presence of a second stimulus can negatively (A) or positively (B) control T cell activation.

[0076] Figure 18 shows schematic representation of gated activation of CAR engineered T cells. If a normal cell that has no stimulus (e.g., an antigen) (Figure 18A) or an antigen that cannot bind to the trans-membrane effector module (Figure18B), or only an antigen that activates the trans-membrane effector module and primes the receiver T cell to express the second effector (Fig 18C), the receiver T cell remains inactive. When both stimuli (e.g. two antigens) that bind the trans-membrane effector module and the primed effector, are present on the presenter cell (e.g. a cancer cell), the T cell is activated (Figure 18D).

[0077] Figure 19A is a bar graph depicting IL12 levels in the various dilutions of media derived from cells expressing DD-IL12. Figure 19B is a bar graph depicting the Shield-1 dose responsive induction of DD- IL12. Figure 19C depicts plasma IL12 levels in mice implanted with SKOV3 cells. Figure 19D depicts plasma IL12 levels in mice in response to different Shield-1 dosing regimens.

[0078] Figure 20A is a western blot of IL15 protein levels in 293 cells. Figure 20B and 20C are histograms depicting surface expression of IL15 and IL15Ra. Figure 20 D is a western blot of IL15 and hDHFR in HCT116 cells.

[0079] Figure 21A and Figure 21B are western blots of depicting the protein levels of CD3 Zeta of the DD- CD19 CAR construct and actin. Figure 21C shows the expression of CD19 chimeric antigen receptors in a western blot using 4-1BB antibody. Figure 21D is a bar graph depicting the surface expression of CD19 CAR.

[0080] Figure 22 denotes the frequency of IFNgamma positive T cells.

[0081] Figure 23A depicts IFN gamma production in T cells. Figure 23B depicts T cell expansion with IL15/IL15Ra treatment. Figure 23C is a dot plot depicting percentage human cells after *in vivo* cell transfer. Figure 23D is scatter plot depicting CD4+/CD8+ T cells.

[0082] Figure 24A depicts T cell subpopulations expressing CD19 CAR. Figure 28B depicts cell death caused by CD19 CAR expressing T cells.

[0083] Figure 25A is a bar graph depicting IL15Ra positive cells with 24 hour TMP treatment. Figure 25B is a bar graph depicting IL15Ra positive cells with 48 hour TMP treatment. Figure 25C is a bar graph depicting IL15Ra positive cells in response to varying concentrations of TMP.

[0084] Figure 26 is a western blot of IL15Ra protein levels in HCT116 cells.

[0085] Figure 27A represents percentage of human T cells blood with respect to mouse T cells. Figure 27B represents the number of T cells in blood. Figure 27C represents ratio of CD4 to CD8 cells in the blood. Figure 27D represents the percentage of IL15Ra positive CD4 and CD8 T cells in the blood.

[0086] Figure 28A depicts the expansion of T cells in response to cytokine treatment. Figure 28B, Figure 28C and Figure 28D depict the frequency of IFN gamma positive cells with IL12 treatment.

[0087] Figure 29 is a bar graph representing the effect of promoters on transgene expression.

[0088] Figure 30A shows the expression of CD19 in parental K562 cells and K562-CD19 cells. Figure 30B shows the proliferation of K562 cells cocultured with T cells expressing DD regulated CAR constructs, in the presence or absence of ligand. Figure 30C shows the area of target cells killed by T cells expressing DD regulated CAR constructs, in the presence of ligand.

[0089] Figure 31A shows IFNgamma concentration. Figure 31B shows IL2 concentration.

[0090] Figure 32A provides the final IL12 concentration for each of the four groups tested. Figure 32B shows that IL12 is detectable in kidney and Figure 32C shows that IL12 is detectable in tumor.

[0091] Figure 33A shows the regulation of IL12 over 24 hours. Figure 33B shows the regulation in the plasma and Figure 33C shows the detection of flexi-IL12 in the kidneys.

[0092] Figure 34A shows that restimulation increased the expression of IL12. Figure 34B and Figure 34C show that ligand increased production of IL12.

[0093] Figure 35A shows the concentration-dependent induction of IL12 secretion of IL12 secretion from primary human T cells. Figure 35B shows the time course induction of IL12 secretion from primary human T cells.

[0094] Figure 36A shows the dose response of Aquashield-Induced DD-IL12 regulation *in vivo*. Figure 36B shows that plasma levels of IL12 remain high in animals transplanted with constitutive IL12 transduced T cells.

[0095] Figure 37A and 37B show the expression of IL12 *in vivo* over 7 days. Figure 37C and 37D show the expression of IL12 *in vivo* over 11 days. Figure 37E shows the Geometric MFI (GeoMFI) of Granzyme B (GrB) after 7 days in CD8+ T cells. Figure 37F shows the GeoMFI of Perforin at day 7 in CD8+ T cells.

[0096] Figure 38A shows the regulation of IL12 with PGK and EF1a promoters and FKBP domains. Figure 38B shows the relative expression of IL12.

[0097] Figure 39 depicts the kinetics of IL15Ra surface expression on CD4 T cells after TMP treatment.

[0098] Figure 40 represents a western blot of IL15-IL15Ra protein in HCT116 tumors from mice treated with TMP for 17 days in xenograft assays.

[0099] Figure 41 is a graph of the results of the MSD assay of IL15 protein levels in HEK293 cells.

[00100] Figure 42A provides FACS plots showing the expression of membrane bound IL15 after a dose response study of TMP. Figure 42B is two graphs showing the dose and time of exposure of TMP *in vitro* influences membrane bound IL15 expression.

[00101] Figures 43A- 43C show the regulation of membrane bound IL15 using IL15 (Figure 43A), IL15Ra (Figure 43B), or IL15/IL15Ra double ++ staining (Figure 43C). Figure 43D shows FACS plots of the expression of IL15. Figure 43E is a graph of the regulation of IL15 in blood and Figure 43F is a graph of the plasma TMP levels.

[00102] Figure 44 represents the regulation of membrane bound IL15 with PO or IP dosing of TMP.

DETAILED DESCRIPTION OF THE INVENTION

[00103] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are now described. Other features, objects and advantages of the invention will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present description will control.

I. INTRODUCTION

[00104] Cancer immunotherapy aims` at the induction or restoration of the reactivity of the immune system towards cancer. Significant advances in immunotherapy research have led to the development of various strategies which may broadly be classified into active immunotherapy and passive immunotherapy. In general, these strategies may be utilized to directly kill cancer cells or to counter the immunosuppressive tumor microenvironment. Active immunotherapy aims at induction of an endogenous, long-lasting tumor-antigen specific immune response. The response can further be enhanced by non-specific stimulation of immune response modifiers such as cytokines. In contrast, passive immunotherapy includes approaches where immune effector molecules such as tumor-antigen specific cytotoxic T cells or antibodies are administered to the host. This approach is short lived and requires multiple applications.

[00105] Despite significant advances, the efficacy of current immunotherapy strategies is limited by associated toxicities. These are often related to the narrow therapeutic window associated with immunotherapy, which in part, emerges from the need to push therapy dose to the edge of potentially fatal toxicity to get a clinically meaningful treatment effect. Further, dose expands *in vivo* since adoptively transferred immune cells continue to proliferate within the patient, often unpredictably.

[00106] A major risk involved in immunotherapy is the on-target but off tumor side effects resulting from T-cell activation in response to normal tissue expression of the tumor associated antigen (TAA). Clinical trials utilizing T cells expressing T-cell receptor against specific TAA reported skin rash, colitis and hearing loss in response to immunotherapy.

[00107] Immunotherapy may also produce on target, on-tumor toxicities that emerge when tumor cells are killed in response to the immunotherapy. The adverse effects include tumor lysis syndrome, cytokine release syndrome and the related macrophage activation syndrome. Importantly, these adverse effects may occur during the destruction of tumors, and thus even a successful on-tumor immunotherapy might result in toxicity. Approaches to regulatably control immunotherapy are thus highly desirable since they have the potential to reduce toxicity and maximize efficacy.

[00108] The present invention provides systems, compositions, immunotherapeutic agents and methods for cancer immunotherapy. These compositions provide tunable regulation of gene expression and function in immunotherapy. The present invention also provides biocircuit systems, effector modules, stimulus response elements (SREs) and payloads, as well as polynucleotides encoding any of the foregoing. In one aspect, the systems, compositions, immunotherapeutic agents and other components of the invention can be controlled by a separately added stimulus, which provides a significant flexibility to regulate cancer immunotherapy. Further, the systems, compositions and the methods of the present invention may also be combined with therapeutic agents such as chemotherapeutic agents, small molecules, gene therapy, and antibodies.

[00109] The tunable nature of the systems and compositions of the invention has the potential to improve the potency and duration of the efficacy of immunotherapies. Reversibly silencing the biological activity of adoptively transferred cells using compositions of the present invention allows maximizing the potential of cell therapy without irretrievably killing and terminating the therapy.

[00110] The present invention provides methods for fine tuning of immunotherapy after administration to patients. This in turn improves the safety and efficacy of immunotherapy and increases the subject population that may benefit from immunotherapy.

II. COMPOSITIONS OF THE INVENTION

[00111] According to the present invention, biocircuit systems are provided which comprise, at their core, at least one effector module system. Such effector module systems comprise at least one effector module having associated, or integral therewith, one or more stimulus response elements (SREs). The overall architecture of a biocircuit system of the invention is illustrated in Figure 1. In general, a stimulus response element (SRE) may be operably linked to a payload construct which could be any protein of interest (POI) (e.g., an immunotherapeutic agent), to form an effector module. The SRE, when activated by a particular stimulus, e.g., a small molecule, can produce a signal or outcome, to regulate transcription and/or protein levels of the linked payload either up or down by perpetuating a stabilizing signal or destabilizing signal, or any other types of regulation. A much-detailed description of a biocircuit system can be found in U.S. Provisional Patent Application No. 62/320,864 filed April 11, 2016 or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587 (the contents of each of which are herein incorporated by reference in their entirety). In accordance with the present invention, biocircuit systems, effector modules, SREs and components that tune expression levels and activities of any agents used for immunotherapy are provided.

[00112] As used herein, a "biocircuit" or "biocircuit system" is defined as a circuit within or useful in biologic systems comprising a stimulus and at least one effector module responsive to a stimulus, where the response to the stimulus produces at least one signal or outcome within, between, as an indicator of, or on a biologic system. Biologic systems are generally understood to be any cell, tissue, organ, organ system or organism, whether animal, plant, fungi, bacterial, or viral. It is also understood that biocircuits may be artificial circuits which employ the stimuli or effector modules taught by the present invention and effect signals or outcomes in acellular environments such as with diagnostic, reporter systems, devices, assays or kits. The artificial circuits may be associated with one or more electronic, magnetic, or radioactive components or parts.

[00113] In accordance with the present invention, a biocircuit system may be a destabilizing domain (DD) biocircuit system, a dimerization biocircuit system, a receptor biocircuit system, and a cell biocircuit system. Any of these systems may act as a signal to any other of these biocircuit systems.

Effector modules and SREs for immunotherapy

[00114] In accordance with the present invention, biocircuit systems, effector modules, SREs, and components that tune expression levels and activities of any agents used for immunotherapy are provided. As non-limiting examples, an immunotherapeutic agent may be an antibody and fragments and variants thereof, a cancer specific T cell receptor (TCR) and variants thereof, an anti-tumor specific chimeric antigen receptor (CAR), a chimeric switch receptor, an inhibitor of a co-inhibitory receptor or ligand, an agonist of a co-stimulatory receptor and ligand, a cytokine, chemokine, a cytokine receptor, a chemokine receptor, a soluble growth factor, a metabolic factor, a suicide gene, a homing receptor, or any agent that induces an immune response in a cell and a subject.

[00115] As stated, the biocircuits of the invention include at least one effector module as a component of an effector module system. As used herein, an "effector module" is a single or multi-component construct or complex comprising at least (a) one or more stimulus response elements (i.e. proteins of interest (POIs). As used herein a "stimulus response element (SRE)" is a component of an effector module which is joined, attached, linked to or associated with one or more payloads of the effector module and in some instances, is responsible for the responsive nature of the effector module to one or more stimuli. As used herein, the "responsive" nature of an SRE to a stimulus may be characterized by a covalent or non-covalent interaction, a direct or indirect association or a structural or chemical reaction to the stimulus. Further, the response of any SRE to a stimulus may be a matter of degree or kind. The response may be a partial response. The response may be a reversible response. The response may ultimately lead to a regulated signal or output. Such output signal may be of a relative nature to the stimulus, e.g., producing a modulatory effect of between 1% and 100% or a factored increase or decrease such as 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more.

[00116] In some embodiments, the present invention provides methods for modulating protein expression, function or level. In some aspects, the modulation of protein expression, function or level refers to modulation of expression, function or level by at least about 20%, such as by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00117] In some embodiments, the present invention provides methods for modulating protein, expression, function or level by measuring the stabilization ratio and destabilization ratio. As used herein, the stabilization ratio may be defined as the ratio of expression, function or level of a protein of interest in response to the stimulus to the expression, function or level of the protein of interest in the absence of the stimulus specific to the SRE. In some aspects, the stabilization ratio is at least 1, such as by at least 1-10, 1-20, 1 -30, 1-40, 1-50, 1- 60, 1-70, 1-80, 1- 90, 1-100, 20-30, 20-40, 20-50, 20-60, 20-70, 20-80, 20-90, 20-95, 20-100, 30-40, 30-50, 30-60, 30-70, 30-80, 30-90, 30-95, 30-100, 40-50, 40-60, 40-70, 40-80, 40-90, 40-95, 40-100, 50-60, 50-70, 50-80, 50-90, 50-95, 50-100, 60-70, 60-80, 60-90, 60-95, 60-100, 70-80, 70-90, 70-95, 70-100, 80-90, 80-95, 80-100, 90-95, 90-100 or 95-100. As used herein, the destabilization ratio may be defined as the ratio of expression, function or level of a protein of interest in the absence of the stimulus specific to the effector module to the expression, function or level of the protein of interest, that is expressed constitutively and in the absence of the stimulus specific to the SRE. As used herein "constitutively" refers to the expression, function or level of a protein of interest that is not linked to an SRE, and is therefore expressed both in the presence and absence of the stimulus. In some aspects, the destabilization ratio is at least 0, such as by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or at least, 0-0.1, 0-0.2, 0 -0.3, 0-0.4, 0-0.5, 0-0.6, 0-0.7, 0-0.8, 0-0.9, 0.1-0.2, 0.1 -0.3, 0.1-0.4, 0.1-0.5, 0.1-0.6, 0.1-0.7, 0.1-0.8, 0.1-0.9, 0.2 -0.3, 0.2-0.4, 0.2-0.5, 0.2-0.6, 0.2-0.7, 0.2-0.8, 0.2-0.9, 0.3-0.4, 0.3-0.5, 0.3-0.6, 0.3-0.7, 0.3-0.8, 0.3-0.9, 0.4-0.5, 0.4-0.6, 0.4-0.7, 0.4-0.8, 0.4-0.9, 0.5-0.6, 0.5-0.7, 0.5-0.8, 0.5-0.9, 0.6-0.7, 0.6-0.8, 0.6-0.9,0.7-0.8, 0.7-0.9 or 0.8-0.9.

[00118] In some embodiments, the stimulus of the present invention maybe ultrasound stimulation. In some embodiments, the SREs of the present invention may derived from mechanosensitive proteins. In one embodiment, the SRE of the present invention may be the mechanically sensitive ion channel, Piezo1.

[00119] Expression of the payload of interest in such instances is tuned by providing focused ultrasound stimulation. In other embodiments, the SREs of the present invention may be derived from calcium biosensors, and the stimulus of the present invention may calcium. The calcium may be generated by the ultrasound induced mechanical stimulation of mechanosensitive ion channels. The ultrasound activation of the ion channel causes a calcium influx thereby generating the stimulus. In one embodiment, the mechanosensitive ion channel is Piezo 1. Mechanosensors may be advantageous to use since they provide spatial control to a specific location in the body.

[00120] The SRE of the effector module may be selected from, but is not limited to, a peptide, peptide complex, peptide-protein complex, protein, fusion protein, protein complex, protein-

protein complex. The SRE may comprise one or more regions derived from any natural or mutated protein, or antibody. In this aspect, the SRE is an element, when responding to a stimulus, can tune intracellular localization, intramolecular activation, and/or degradation of payloads.

[00121] In some embodiments, effector modules of the present invention may comprise additional features that facilitate the expression and regulation of the effector module, such as one or more signal sequences (SSs), one or more cleavage and/or processing sites, one or more targeting and/or penetrating peptides, one or more tags, and/or one or more linkers. Additionally, effector modules of the present invention may further comprise other regulatory moieties such as inducible promoters, enhancer sequences, microRNA sites, and/or microRNA targeting sites. Each aspect or tuned modality may bring to the effector module or biocircuit a differentially tuned feature. For example, an SRE may represent a destabilizing domain, while mutations in the protein payload may alter its cleavage sites or dimerization properties or half-life and the inclusion of one or more microRNA or microRNA binding site may impart cellular detargeting or trafficking features. Consequently, the present invention embraces biocircuits which are multifactorial in their tenability. Such biocircuits may be engineered to contain one, two, three, four or more tuned features.

[00122] In some embodiments, effector modules of the present invention may include one or more degrons to tune expression. As used herein, a "degron" refers to a minimal sequence within a protein that is sufficient for the recognition and the degradation by the proteolytic system. An important property of degrons is that they are transferrable, that is, appending a degron to a sequence confers degradation upon the sequence. In some embodiments, the degron may be appended to the destabilizing domains, the payload or both. Incorporation of the degron within the effector module of the invention, confers additional protein instability to the effector module and may be used to minimize basal expression. In some embodiments, the degron may be an N-degron, a phospho degron, a heat inducible degron, a photosensitive degron, an oxygen dependent degron. As a non-limiting example, the degron may be an Ornithine decarboxylase degron as described by Takeuchi et al. (Takeuchi J et al. (2008). Biochem J. 2008 Mar 1;410(2):401-7; the contents of which are incorporated by reference in their entirety). Other examples of degrons useful in the present invention include degrons described in International patent publication Nos. WO2017004022, WO2016210343, and WO2011062962; the contents of each of which are incorporated by reference in their entirety.

[00123] As shown in Figure 2, representative effector module embodiments comprising one payload, i.e. one immunotherapeutic agent are illustrated. Each components of the effector

module may be located or positioned in various arrangements without (A to F) or with (G to Z, and AA to DD) a cleavage site. An optional linker may be inserted between each component of the effector module.

[00124] Figures 3 to 6 illustrate representative effector module embodiments comprising two payloads, i.e. two immunotherapeutic agents. In some aspects, more than two immunotherapeutic agents (payloads) may be included in the effector module under the regulation of the same SRE (e.g., the same DD). The two or more agents may be either directly linked to each other or separated (Figure 3). The SRE may be positioned at the N-terminus of the construct, or the C-terminus of the construct, or in the internal location.

[00125] In some aspects, the two or more immunotherapeutic agents may be the same type such as two antibodies, or different types such as a CAR construct and a cytokine IL12. Biocircuits and components utilizing such effector molecules are given in Figures 7-12.

[00126] In some embodiments, biocircuits of the invention may be modified to reduce their immunogenicity. Immunogenicity is the result of a complex series of responses to a substance that is perceived as foreign and may include the production of neutralizing and non-neutralizing antibodies, formation of immune complexes, complement activation, mast cell activation, inflammation, hypersensitivity responses, and anaphylaxis. Several factors can contribute to protein immunogenicity, including, but not limited to protein sequence, route and frequency of administration and patient population. In a preferred embodiment, protein engineering may be used to reduce the immunogenicity of the compositions of the invention. In some embodiments, modifications to reduce immunogenicity may include modifications that reduce binding of the processed peptides derived from the parent sequence to MHC proteins. For example, amino acid modifications may be engineered such that there are no or a minimal of number of immune epitopes that are predicted to bind with high affinity, to any prevalent MHC alleles. Several methods of identifying MHC binding epitopes of known protein sequences are known in the art and may be used to score epitopes in the compositions of the present invention. Such methods are disclosed in US Patent Publication No. US 20020119492, US20040230380, and US 20060148009; the contents of each of which are incorporated by reference in their entirety.

[00127] Epitope identification and subsequent sequence modification may be applied to reduce immunogenicity. The identification of immunogenic epitopes may be achieved either physically or computationally. Physical methods of epitope identification may include, for example, mass spectrometry and tissue culture/cellular techniques. Computational approaches that utilize information obtained on antigen processing, loading and display, structural and/or proteomic data toward identifying non-self-peptides that may result from antigen processing, and that are

likely to have good binding characteristics in the groove of the MHC may also be utilized. One or more mutations may be introduced into the biocircuits of the invention directing the expression of the protein, to maintain its functionality while simultaneously rendering the identified epitope less or non-immunogenic.

[00128] In some embodiments, protein modifications engineered into the structure of the compositions of the invention to interfere with antigen processing and peptide loading such as glycosylation and PEGylation, may also be useful in the present invention. Compositions of the invention may also be engineered to include non-classical amino acid sidechains to design less immunogenic compositions. Any of the methods discussed in International Patent Publication No. WO2005051975 for reducing immunogenicity may be useful in the present invention (the contents of which are incorporated by reference in their entirety).

[00129] In one embodiment, patients may also be stratified according to the immunogenic peptides presented by their immune cells and may be utilized as a parameter to determine suitable patient cohorts that may therapeutically benefit for the compositions of the invention.

[00130] In some embodiments, reduced immunogenicity may be achieved by limiting immuproteasome processing. The proteasome is an important cellular protease that is found in two forms: the constitutive proteasome, which is expressed in all cell types and which contains active e.g. catalytic subunits and the immunoproteasome that is expressed in cell of the hematopoietic lineage, and which contains different active subunits termed low molecular weight proteins (LMP) namely LMP-2, LMP- 7 and LMP-10. Immunoproteasomes exhibit altered peptidase activities and cleavage site preferences that result in more efficient liberation of many MHC class I epitopes. A well described function of the immunoproteasome is to generate peptides with hydrophobic C terminus that can be processed to fit in the groove of MHC class I molecules. Deol P et al. have shown that immunoproteasomes may lead to a frequent cleavage of specific peptide bonds and thereby to a faster appearance of a certain peptide on the surface of the antigen presenting cells; and enhanced peptide quantities (Deol P et al. (2007) *J Immunol* 178 (12) 7557-7562; the contents of which are incorporated herein reference in its entirety). This study indicates that reduced immunoproteasome processing may be accompanied by reduced immunogenicity. In some embodiments, immunogenicity of the compositions of the invention may be reduced by modifying the sequence encoding the compositions of the invention to prevent immunoproteasome processing. Biocircuits of the present invention may also be combined with immunoproteasome-selective inhibitors to achieve the same effects. Examples of inhibitors useful in the present invention include UK-101 (B1i selective compound), IPSI-001, ONX 0914 (PR-957), and PR-924 (IPSI).

1. Destabilizing domains (DDs)

[00131] In some embodiments, biocircuit systems, effector modules, and compositions of the present invention relate to post-translational regulation of protein (payload) function anti-tumor immune responses of immunotherapeutic agents. In one embodiment, the SRE is a stabilizing/destabilizing domain (DD). The presence, absence or an amount of a small molecule ligand that binds to or interacts with the DD, can, upon such binding or interaction modulate the stability of the payload(s) and consequently the function of the payload. Depending on the degree of binding and/or interaction the altered function of the payload may vary, hence providing a "tuning" of the payload function.

[00132] In some embodiments, destabilizing domains described herein or known in the art may be used as SREs in the biocircuit systems of the present invention in association with any of the immunotherapeutic agents (payloads) taught herein. Destabilizing domains (DDs) are small protein domains that can be appended to a target protein of interest. DDs render the attached protein of interest unstable in the absence of a DD-binding ligand such that the protein is rapidly degraded by the ubiquitin-proteasome system of the cell (Stankunas, K., et al., Mol. Cell, 2003, 12: 1615–1624; Banaszynski, *et al.*, Cell; 2006, 126(5): 995–1004; reviewed in Banaszynski, L.A., and Wandless, T.J. *Chem. Biol.*; 2006, 13:11–21 and Rakhit R et al., *Chem Biol.* 2014; 21(9):1238-1252). However, when a specific small molecule ligand binds its intended DD as a ligand binding partner, the instability is reversed and protein function is restored. The conditional nature of DD stability allows a rapid and non-perturbing switch from stable protein to unstable substrate for degradation. Moreover, its dependency on the concentration of its ligand further provides tunable control of degradation rates.

[00133] In some embodiments, the desired characteristics of the DDs may include, but are not limited to, low protein levels in the absence of a ligand of the DD (i.e. low basal stability), large dynamic range, robust and predictable dose-response behavior, and rapid kinetics of degradation. DDs that bind to a desired ligand but not endogenous molecules may be preferred.

[00134] Several protein domains with destabilizing properties and their paired small molecules have been identified and used to control protein expression, including FKBP/shield-1 system (Egeler et al., *J Biol. Chem.* 2011, 286(36): 32328-31336; the contents of which are incorporated herein by reference in their entirety), ecDHFR and its ligand trimethoprim (TMP); estrogen receptor domains which can be regulated by several estrogen receptor antagonists (Miyazaki et al., *J Am Chem. Soc.*, 2012, 134(9): 3942-3945; the contents of which are incorporated by reference herein in their entirety); and fluorescent destabilizing domain (FDD) derived from

bilirubin-inducible fluorescent protein, UnaG and its cognate ligand bilirubin (BR) (Navarro et al., *ACS Chem Biol.*, 2016, June 6; the contents of which are incorporated herein by reference in their entirety).

[00135] Known DDs also include those described in U.S. Pat. NO. 8,173,792 and U.S. Pat. NO. 8,530,636, the contents of which are each incorporated herein by reference in their entirety.

[00136] In some embodiments, the DDs of the present invention may be derived from some known sequences that have been approved to be capable of post-translational regulation of proteins. For example, Xiong et al., have demonstrated that the non-catalytic N-terminal domain (54-residues) of ACS7 (1-aminocyclopropane-1-carboxylate synthase) in *Arabidopsis*, when fused to the β-glucuronidase (GUS) reporter, can significantly decrease the accumulation of the GUS fusion protein (Xiong et al., *J. Exp. Bot.*, 2014, 65(15): 4397-4408). Xiong et al. further demonstrated that both exogenous 1-aminocyclopropane-1-carboxylic acid (ACC) treatment and salt can rescue the levels of accumulation of the ACS N-terminal and GUS fusion protein. The ACS N-terminus mediates the regulation of ACS7 stability through the ubiquitin–26S proteasome pathway.

[00137] Another non-limiting example is the stability control region (SCR, residues 97-118) of Tropomyosin (Tm), which controls protein stability. A destabilizing mutation L110A, and a stabilizing mutation A109L dramatically affect Tropomyosin protein dynamics (Kirwan and Hodges, *J. Biol. Chem.*, 2014, 289: 4356-4366). Such sequences can be screened for ligands that bind them and regulate their stability. The identified sequence and ligand pairs may be used as components of the present invention.

[00138] In some embodiments, the DDs of the present invention may be developed from known proteins. Regions or portions or domains of wild type proteins may be utilized as SREs/DDs in whole or in part. They may be combined or rearranged to create new peptides, proteins, regions or domains of which any may be used as SREs/DDs or the starting point for the design of further SREs and/or DDs.

[00139] Ligands such as small molecules that are well known to bind candidate proteins can be tested for their regulation in protein responses. The small molecules may be clinically approved to be safe and have appropriate pharmaceutical kinetics and distribution. In some embodiments, the stimulus is a ligand of a destabilizing domain (DD), for example, a small molecule that binds a destabilizing domain and stabilizes the POI fused to the destabilizing domain. In some embodiments, ligands, DDs and SREs of the present invention, include without limitation, any of those taught in Tables 2-4 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed

March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety. Some examples of the proteins that may be used to develop DDs and their ligands are listed in Table 1.

Table 1: Proteins and their binding ligands

Protein	Protein Sequence	Protein SEQ ID NO.:	Ligands
E. coli Dihydrofolate reductase (ecDHFR) (Uniprot ID: P0ABQ4)	MISLIAALAVDRVIGMENAMPWNLPADL AWFKRNTLNKPVIMGRHTWESIGRPLPGR KNIILSSQPGTDDRVTWVKSVDEAIAACG DVPEIMVIGGGRVYEQFLPKAQKLYLTHI DAEVEGDTHFPDYEPDDWESVFSEFHDA DAQNSHSYCFEILERR	1	Methotrexate (MTX) Trimethoprim (TMP)
Human Dihydrofolate reductase (hDHFR) (Uniprot ID: P00374)	MVGSLNCIVAVSQNMGIGKNGDLPWPPL RNEFRYFQRMTTTSSVEGKQNLVIMGKK TWFSIPEKNRPLKGRINLVLSRELKEPPQG AHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDF ESDTFFPEIDLEKYKLLPEYPGVLSDVQEE KGIKYKFEVYEKND	2	Methotrexate (MTX) Trimethoprim (TMP)
FK506 binding protein (FKBP) (Uniprot ID: P62942)	GVQVETISPGDGRTFPKRGQTCVVHYTG MLEDGKKFDSSRDRNKPFKFMLGKQEVI RGWEEGVAQMSVGQRAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLKLE	3	Shield-1
Phosphodiesterase 5 (PDE5), ligand binding domain (Uniprot ID: Uniprot ID O76074)	MEETRELQSLAAAVVPSAQTLKITDFSFS DFELSDLETALCTIRMFTDLNLVQNFQMK HEVLCRWILSVKKNYRKNVAYHNWRHA FNTAQCMFAALKAGKIQNKLTDLEILALL IAALSHDLDHRGVNNSYIQRSEHPLAQLY CHSIMEHHHFDQCLMILNSPGNQILSGLSI EEYKTTLKIIKQAILATDLALYIKRRGEFFE LIRKNQFNLEDPHQKELFLAMLMTACDLS AITKPWPIQQRIAELVATEFFDQGDRERKE LNIEPTDLMNREKKNKIPSMQVGFIDAICL QLYEALTHVSEDCFPLLDGCRKNRQKWQ ALAEQQ	4	Sildenafil; Vardenafil; Tadalafil
PPAR gamma, ligand binding domain (Uniprot ID: P37231; amino acids 317-505)	SVEAVQEITEYAKSIPGFVNLDLNDQVTL LKYGVHEIIYTMLASLMNKDGVLISEGQG FMTREFLKSLRKPFGDFMEPKFEFAVKFN ALELDDSDLAIFIAVIILSGDRPGLLNVKPI EDIQDNLLQALELQLKLNHPESSQLFAKL LQKMTDLRQIVTEHVQLLQVIKKTETDMS LHPLLQEIYKDLY	5	Posiglitazone Pioglitazone
Carbonic anhydrase II (CA2) (Uniprot ID: P00918)	MSHHWGYGKHNGPEHWHKDFPIAKGER QSPVDIDTHTAKYDPSLKPLSVSYDQATS LRILNNGHAFNVEFDDSQDKAVLKGGPL DGTYRLIQFHFHWGSLDGQGSEHTVDKK KYAAELHLVHWNTKYGDFGKAVQQPDG LAVLGIFLKVGSAKPGLQKVVDVLDSIKT KGKSADFTNFDPRGLLPESLDYWTYPGSL TTPPLLECVTWIVLKEPISVSSEQVLKFRK LNFNGEGEPEELMVDNWRPAQPLKNRQI KASFK	6	Celecoxib Acetazolamide
NRH: Quinone oxidoreductase 2 (NQO2) (Uniprot ID: P16083)	MAGKKVLIVYAHQEPKSFNGSLKNVAVD ELSRQGCTVTVSDLYAMNLEPRATDKDIT GTLSNPEVFNYGVETHEAYKQRSLASDIT DEQKKVREADLVIFQFPLYWFSVPAILKG	7	Imatinib Melatonin

	WMDRVLCQGFAFDIPGFYDSGLLQGKLA LLSVTTGGTAEMYTKTGVNGDSRYFLWP LQHGTLHFCGFKVLAPQISFAPEIASEEER KGMVAAWSQRLQTIWKEEPIPCTAHWHF GQ		

[00140] In some embodiments, DDs of the invention may be FKBP DD or ecDHFR DDs such as those listed in Table 2. The position of the mutated amino acid listed in Table 2 is relative to the ecDHFR (Uniprot ID: P0ABQ4) of SEQ ID NO. 1 for ecDHFR DDs and relative to FKBP (Uniprot ID: P62942) of SEQ ID NO. 3 for FKBP DDs.

Table 2: ecDHFR DDs and FKBP DDs

DD	Sequence	SEQ ID NO:
ecDHFR (R12Y, Y100I)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLY LTHIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNS HSYCFEILERR	8
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLN KPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWV KSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLT HIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHS YCFEILERR	9
ecDHFR (Amino acid 2-159 of WT) (R12H, E129K)	ISLIAALAVDHVIGMENAMPWNLPADLAWFKRNTLN KPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWV KSVDEAIAACGDVPEIMVIGGGRVYEQFLPKAQKLYL THIDAEVEGDTHFPDYKPDDWESVFSEFHDADAQNSH SYCFEILERR	10
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRA KLTISPDYAYGATGHPGIIPPHATLVFDVELLKPE	11
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQGA KLTISPDYAYGATGHPGIIPPHATLVFDVELLELE	12

[00141] Inventors of the present invention have tested and identified several candidate human proteins that may be used to develop destabilizing domains. As show in Table 2, these candidates include human DHFR (hDHFR), PDE5 (phosphodiesterase 5), PPAR gamma (peroxisome proliferator-activated receptor gamma), CA2 (Carbonic anhydrase II) and NQO2 (NRH: Quinone oxidoreductase 2). Candidate destabilizing domain sequence identified from protein domains of these proteins (as a template) may be mutated to generate libraries of mutants based on the template candidate domain sequence. Mutagenesis strategies used to generate DD libraries may include site-directed mutagenesis e.g. by using structure guided information; or random mutagenesis e.g. using error-prone PCR, or a combination of both. In some embodiments, destabilizing domains identified using random mutagenesis may be used to identify structural

properties of the candidate DDs that may be required for destabilization, which may then be used to further generate libraries of mutations using site directed mutagenesis.

[00142] In some embodiments, novel DDs derived from E.coli DHFR (ecDHFR) may comprise amino acids 2-159 of the wild type ecDHFR sequence. This may be referred to as an M1del mutation.

[00143] In some embodiments, novel DDs derived from ecDHFR may comprise amino acids 2-159 of the wild type ecDHFR sequence (also referred to as an M1del mutation), and may include one, two, three, four, five or more mutations including, but not limited to, M1del, R12Y, R12H, Y100I, and E129K.

[00144] In some embodiments, novel DDs derived from FKBP may comprise amino acids 2-107 of the wild type FKBP sequence. This may be referred to as an M1del mutation.

[00145] In some embodiments, novel DDs derived from FKBP may comprise amino acids 2-107 of the wild type FBKP sequence (also referred to as an M1del mutation), and may include one, two, three, four, five or more mutations including, but not limited to, M1del, E31G, F36V, R71G, K105E, and L106P.

[00146] In some embodiments, DD mutant libraries may be screened for mutations with altered, preferably higher binding affinity to the ligand, as compared to the wild type protein. DD libraries may also be screened using two or more ligands and DD mutations that are stabilized by some ligands but not others may be preferentially selected. DD mutations that bind preferentially to the ligand compared to a naturally occurring protein may also be selected. Such methods may be used to optimize ligand selection and ligand binding affinity of the DD. Additionally, such approaches can be used to minimize deleterious effects caused by off-target ligand binding.

[00147] In some embodiments, suitable DDs may be identified by screening mutant libraries using barcodes. Such methods may be used to detect, identify and quantify individual mutant clones within the heterogeneous mutant library. Each DD mutant within the library may have distinct barcode sequences (with respect to each other). In other instances, the polynucleotides can also have different barcode sequences with respect to 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleic acid bases. Each DD mutant within the library may also comprise a plurality of barcode sequences. When used in plurality may be used such that each barcode is unique to any other barcode. Alternatively, each barcode used may not be unique, but the combination of barcodes used may create a unique sequence that can be individually tracked. The barcode sequence may be placed upstream of the SRE, downstream of the SRE, or in some instances may be placed within the SRE. DD mutants may be identified by barcodes using sequencing approaches such as Sanger sequencing, and next generation sequencing, but also by polymerase chain reaction and

quantitative polymerase chain reaction. In some embodiments, polymerase chain reaction primers that amplify a different size product for each barcode may be used to identify each barcode on an agarose gel. In other instances, each barcode may have a unique quantitative polymerase chain reaction probe sequence that enables targeted amplification of each barcode.

[00148] In some embodiments, DDs of the invention may be derived from human dihydrofolate reductase (hDHFR). hDHFR is a small (18 kDa) enzyme that catalyzes the reduction of dihydrofolate and plays a vital role in variety of anabolic pathway. Dihydrofolate reductase (DHFR) is an essential enzyme that converts 7,8-dihydrofolate (DHF) to 5,6,7,8, tetrahydrofolate (THF) in the presence of nicotinamide adenine dihydrogen phosphate (NADPH). Anti-folate drugs such as methotrexate (MTX), a structural analogue of folic acid, which bind to DHFR more strongly than the natural substrate DHF, interferes with folate metabolism, mainly by inhibition of dihydrofolate reductase, resulting in the suppression of purine and pyrimidine precursor synthesis. Other inhibitors of hDHFR such as folate, TQD, Trimethoprim (TMP), epigallocatechin gallate (EGCG) and ECG (epicatechin gallate) can also bind to hDHFR mutants and regulates its stability.In one aspect of the invention, the DDs of the invention may be hDHFR mutants including the single mutation hDHFR (Y122I), hDHFR (K81R), hDHFR (F59S), hDHFR (I17V), hDHFR (N65D), hDHFR (A107V), hDHFR (N127Y), hDHFR (K185E), hDHFR (N186D), and hDHFR (M140I); double mutations: hDHFR (M53T, R138I), hDHFR (V75F, Y122I), hDHFR (A125F, Y122I), hDHFR (L74N, Y122I), hDHFR (L94A, T147A), hDHFR (G21T, Y122I), hDHFR (V121A, Y122I), hDHFR (Q36K, Y122I), hDHFR (C7R, Y163C),hDHFR (Y178H, E18IG), hDHFR (A10V, H88Y), hDHFR (T137R, F143L), hDHFR (E63G, I176F), hDHFR (T57A, I72A), hDHFR (H131R, E144G), and hDHFR (Y183H, K185E); and triple mutations: hDHFR (Q36F, N65F, Y122I), hDHFR (G21E, I72V, I176T), hDHFR (I8V, K133E, Y163C), hDHFR (V9A, S93R, P150L), hDHFR (K19E, F89L, E181G), hDHFR (G54R, M140V, S168C), hDHFR (L23S, V121A, Y157C), hDHFR (V110A, V136M, K177R), and hDHFR (N49D, F59S, D153G).

[00149] In one embodiment, the stimulus is a small molecule that binds to a SRE to post-translationally regulate protein levels. In one aspect, DHFR ligands: trimethoprim (TMP) and methotrexate (MTX) are used to stabilize hDHFR mutants. The hDHFR based destabilizing domains are listed in Table 3. The position of the mutated amino acid listed in Table 3 is relative to the human DHFR (Uniprot ID: P00374) of SEQ ID NO. 2 for human DHFR. In Table 3, "del" means that the mutation is the deletion of the amino acid at that position relative to the wild type sequence.

Table 3: Human DHFR mutants and novel destabilizing domains

Mutants	Amino acid Sequence	SEQ ID NO
hDHFR (I17V)	MVGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	13
hDHFR (F59S)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWSSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	14
hDHFR (N65D)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKDRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	15
hDHFR (K81R)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELREPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	16
hDHFR (A107V)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELVNKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	17
hDHFR (Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	18
hDHFR (N127Y)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMYHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	19
hDHFR (M140I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIIQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	20
hDHFR (K185E)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEEND	21
hDHFR (N186D)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKDD	22
hDHFR (C7R, Y163C)	MVGSLNRIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPECPGVLSDVQEEKGIKYKFEVYEKND	23

hDHFR (A10V, H88Y)	MVGSLNCIVVVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAYFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	24
hDHFR (Q36K, Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFKR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	25
hDHFR (M53T, R138I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVITGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTIIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	26
hDHFR (T57A, I72A)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKAWFSIPEKNRPLKGRANLV LSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMV WIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEI DLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	27
hDHFR (E63G, I176F)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPGKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGFKYKFEVYEKND	28
hDHFR (G21T, Y122I)	MVGSLNCIVAVSQNMGIGKNTDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	29
hDHFR (L74N, Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINNVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	30
hDHFR (V75F, Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLFL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	31
hDHFR (L94A, T147A)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSADDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDAFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	32
DHFR (V121A, Y22I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSAIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	33
hDHFR (Y122I, A125F)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVIKEFMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	34
hDHFR (H131R, E144G)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGRLKLFVTRIMQDFGSDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	35

hDHFR (T137R, F143L)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVRRIMQDLESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	36
hDHFR (Y178H, E18IG)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKHKFGVYEKND	37
hDHFR (Y183H, K185E)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVHEEND	38
hDHFR (V9A, S93R, P150L)	MVGSLNCIAAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRRLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFLEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	39
hDHFR (I8V, K133E, Y163C)	MVGSLNCVVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLELFVTRIMQDFESDTFFPEID LEKYKLLPECPGVLSDVQEEKGIKYKFEVYEKND	40
hDHFR (L23S, V121A, Y157C)	MVGSLNCIVAVSQNMGIGKNGDSPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSAYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKCKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	41
hDHFR (K19E, F89L, E181G)	MVGSLNCIVAVSQNMGIGENGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHLLSRSLDDALKLTEQPELANKVDMVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFGVYEKND	42
hDHFR (Q36F, N65F, Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFFRM TTTSSVEGKQNLVIMGKKTWFSIPEKFRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	43
hDHFR (G54R, M140V, S168C)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMRKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIVQDFESDTFFPEIDL EKYKLLPEYPGVLCDVQEEKGIKYKFEVYEKND	44
hDHFR (V110A, V136M, K177R)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKADMVW IVGGSSVYKEAMNHPGHLKLFMTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIRYKFEVYEKND	45
hDHFR (Amino acid 2-187 of WT; Q36F, Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFFRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEFMNHPGHLKLFVTRIMQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	46
hDHFR (N49D, F59S, D153G)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQDLVIMGKKTWSSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIG LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	47

hDHFR (G21E, I72V, I176T)	MVGSLNCIVAVSQNMGIGKNEDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRVNLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGTKYKFEVYEKND	48
hDHFR (L100P, E102G, Q103R, P104S, E105G, N108D, V113A, W114R, Y122C, M126I, N127R, H128Y, L132P, F135P, I139T, F148S, F149L, I152V, D153A, D169G, V170A, I176A, K177R, V182A, K185R, N186S)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKPTGRSGLADKVDMAR IVGGSSVCKEAIRYPGHPKLPVTRTMQDFESDTSLPEVA LEKYKLLPEYPGVLSGAQEEKGARYKFEAYERSD	871
hDHFR (V2A, R33G, Q36R, L100P, K185R)	MAGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFGYFRR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKPTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYERND	872
hDHFR (G16S, I17V, F89L, D96G, K123E, M140V, D146G, K156R)	MVGSLNCIVAVSQNMSVGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHLLSRSLDGALKLTEQPELANKVDMVW IVGGSSVYEEAMNHPGHLKLFVTRIVQDFESGTFFPEIDL ERYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	873
hDHFR (F35L, R37G, N65A, L68S, K69E, R71G, L80P, K99G, G117D, L132P, I139V, M140I, D142G, D146G, E173G, D187G)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYLQG MTTTSSVEGKQNLVIMGKKTWFSIPEKARPSEGGINLVL SREPKEPPQGAHFLSRSLDDALGLTEQPELANKVDMVW IVDGSSVYKEAMNHPGHPKLFVTRVIQGFESGTFFPEIDL EKYKLLPEYPGVLSDVQEGKGIKYKFEVYEKNG	874
hDHFR (I17N, L98S, K99R, M112T, E151G, E162G, E172G)	MVGSLNCIVAVSQNMGNGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDASRLTEQPELANKVDTVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPGIDL EKYKLLPGYPGVLSDVQGEKGIKYKFEVYEKND	875
hDHFR (R138G, D142G, F143S, K156R, K158E, E162G, V166A, K177E, Y178C, K185E, N186S)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTGIMQGSESDTFFPEID LERYELLPGYPGALSDVQEEKGIECKFEVYEESD	876
hDHFR (K81R, K99R, L100P, E102G, N108D, K123R, H128R, D142G, F180L, K185E)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELREPPQGAHFLSRSLDDALRPTGQPELADKVDMVW IVGGSSVYREAMNRPGHLKLFVTRIMQGFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKLEVYEEND	877
hDHFR (N14S, P24S, F35L, M53T, K56E, R92G, S93G, N127S, H128Y, F135L, F143S, L159P, L160P, E173A, F180L)	MVGSLNCIVAVSQSMGIGKNGDLSWPPLRNEFRYLQRM TTTSSVEGKQNLVITGKETWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSGGLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMSYPGHLKLLVTRIMQDSESDTFFPEIDLE KYKPPPEYPGVLSDVQEAKGIKYKLEVYEKND	878
hDHFR (V2A, I17V, N30D, E31G, Q36R, F59S, K69E, I72T, H88Y, F89L, N108D, K109E, V110A, I115V, Y122D, L132P, F135S, M140V, E144G, T147A, Y157C, V170A, K174R, N186S)	MAGSLNCIVAVSQNMGVGKNGDLPWPPLRDGFRYFRR MTTTSSVEGKQNLVIMGKKTWSSIPEKNRPLEGRTNLV LSRELKEPPQGAYLLSRSLDDALKLTEQPELADEAGMV WVVGGSSVDKEAMNHPGHPKLSVTRIVQDFGSDAFFPE IDLEKCKLLPEYPGVLSDAQEERGIKYKFEVYEKSD	879
hDHFR (L28P, N30H, M38V, V44A, L68S, N73G, R78G, A97T, K99R, A107T, K109R, D111N, L134P, F135V, T147A, I152V, K158R, E172G, V182A, E184R)	MVGSLNCIVAVSQNMGIGKNGDLPWPPPRHEFRYFQRV TTTSSAEGKQNLVIMGKKTWFSIPEKNRPSKGRIGLVLS GELKEPPQGAHFLSRSLDDTLRLTEQPELTNRVNMVWI VGGSSVYKEAMNHPGHLRPVVTRIMQDFESDAFFPEVD LEKYRLLPEYPGVLSDVQGEKGIKYKFEAYRKND	880
hDHFR (A10T, Q13R, N14S, N20D, P24S, N30S, M38T, T40A,	MVGSLNCIVTVSRSMGIGKDGDLSWPPLRSEFRYFQRTT ATSSVEGRQSLVIMGKRTWFSTPERNRPLRGRANLVLS	881

K47R, N49S, K56R, I61T, K64R, K69R, I72A, R78G, E82G, F89L, D96G, N108D, M112V, W114R, Y122D, K123E, I139V, Q141R, D142G, F148L, E151G, E155G, Y157R, Q171R, Y183C, E184G, K185del, D187N)	GELKGPPQGAHLLSRSLDGALKLTEQPELADKVDVVRI VGGSSVDEEAMNHPGHLKLFVTRVMRGFESDTLFPGID LGKRKLLPEYPGVLSDVREEKGIKYKLEVCGNN	
hDHFR (Amino acid 2-187 of WT; I17V, Y122I)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	882
hDHFR (Amino acid 2-187 of WT; Y122I, M140I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIIQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	883
hDHFR (Amino acid 2-187 of WT; N127Y, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMYHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	884
hDHFR (Amino acid 2-187 of WT; Y122I, H131R, E144G)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGRLKLFVTRIMQDFGSDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	885
hDHFR (Amino acid 2-187 of WT; D22S, F32M, R33S, Q36S, N65S)	VGSLNCIVAVSQNMGIGKNGSLPWPPLRNEMSYFSRMT TTSSVEGKQNLVIMGKKTWFSIPEKSRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	886
hDHFR (Amino acid 2-187 of WT; E31D, F32M, V116I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNDMRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWII GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	887
hDHFR (Amino acid 2-187 of WT; E162G, I176F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPGYPGVLSDVQEEKGFKYKFEVYEKND	888
hDHFR (Amino acid 2-187 of WT; K185E)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEEND	889
hDHFR (Amino acid 2-187 of WT; Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEFMNHPGHLKLFVTRIMQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	890
hDHFR (Amino acid 2-187 of WT; Q36F, N65F, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFFRMT TTSSVEGKQNLVIMGKKTWFSIPEKFRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	891
hDHFR (Amino acid 2-187 of WT; N127Y)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV	892

	GGSSVYKEAMYHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	
hDHFR (Amino acid 2-187 of WT; H131R, E144G)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGRLKLFVTRIMQDFGSDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	893
hDHFR (Amino acid 2-187 of WT; I17V)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	894
hDHFR (Amino acid 2-187 of WT; Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	895
hDHFR (E162G, I176F)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPGYPGVLSDVQEEKGFKYKFEVYEKND	896
hDHFR (Amino acid 2-187 of WT; Q36K, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFKRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	981

[00150] In some embodiments, DD mutations that do not inhibit ligand binding may be preferentially selected. In some embodiments, ligand binding may be improved by mutation of residues in DHFR. Amino acid positions selected for mutation include aspartic acid at position 22 of SEQ ID NO. 2, glutamic acid at position 31 of SEQ ID NO. 2; phenyl alanine at position 32 of SEQ ID NO. 2; arginine at position 33 of SEQ ID NO. 2; glutamine at position 36 of SEQ ID NO. 2; asparagine at position 65 of SEQ ID NO. 2; and valine at position 115 of SEQ ID NO. 2. In some embodiments, one or more of the following mutations may be utilized in the DDs of the present invention to improve TMP binding, including but not limited to, D22S, E31D, F32M, R33S, Q36S, N65S, and V116I. The position of the mutated amino acids is relative to the wildtype human DHFR (Uniprot ID: P00374) of SEQ ID NO. 2.

[00151] In some embodiments, novel DDs derived from human DHFR may include one, two, three, four, five or more mutations including, but not limited to, M1del, V2A, C7R, I8V, V9A, A10T, A10V, Q13R, N14S, G16S, I17N, I17V, K19E, N20D, G21T, G21E, D22S, L23S, P24S, L28P, N30D, N30H, N30S, E31G, E31D, F32M, R33G, R33S, F35L, Q36R, Q36S, Q36K, Q36F, R37G, M38V, M38T, T40A, V44A, K47R, N49S, N49D, M53T, G54R, K56E, K56R, T57A, F59S, I61T, K64R, N65A, N65S, N65D, N65F, L68S, K69E, K69R, R71G, I72T, I72A, I72V, N73G, L74N, V75F, R78G, L80P, K81R, E82G, H88Y, F89L, R92G, S93G, S93R, L94A, D96G, A97T, L98S, K99G, K99R, L100P, E102G, Q103R, P104S, E105G, A107T, A107V,

N108D, K109E, K109R, V110A, D111N, M112T, M112V, V113A, W114R, I115V, I115L, V116I, G117D, V121A, Y122C, Y122D, Y122I, K123R, K123E, A125F, M126I, N127R, N127S, N127Y, H128R, H128Y, H131R, L132P, K133E, L134P, F135P, F135L, F135S, F135V, V136M, T137R, R138G, R138I, I139T, I139V, M140I, M140V, Q141R, D142G, F143S, F143L, E144G, D146G, T147A, F148S, F148L, F149L, P150L, E151G, I152V, D153A, D153G, E155G, K156R, Y157R, Y157C, K158E, K158R, L159P, L160P, E162G, Y163C, V166A, S168C, D169G, V170A, Q171R, E172G, E173G, E173A, K174R, I176A, I176F, I176T, K177E, K177R, Y178C, Y178H, F180L, E181G, V182A, Y183C, Y183H, E184R, E184G, K185R, K185del, K185E, N186S, N186D, D187G, and D187N.

[00152] In some embodiments, novel DDs derived from human DHFR may comprise amino acids 2-187 of the wild type human DHFR sequence. This may be referred to as an M1del mutation.

[00153] In some embodiments, novel DDs derived from human DHFR may comprise amino acids 2-187 of the wild type human DHFR sequence (also referred to as an M1del mutation), and may include one, two, three, four, five or more mutations including, but not limited to, M1del, V2A, C7R, I8V, V9A, A10T, A10V, Q13R, N14S, G16S, I17N, I17V, K19E, N20D, G21T, G21E, D22S, L23S, P24S, L28P, N30D, N30H, N30S, E31G, E31D, F32M, R33G, R33S, F35L, Q36R, Q36S, Q36K, Q36F, R37G, M38V, M38T, T40A, V44A, K47R, N49S, N49D, M53T, G54R, K56E, K56R, T57A, F59S, I61T, K64R, N65A, N65S, N65D, N65F, L68S, K69E, K69R, R71G, I72T, I72A, I72V, N73G, L74N, V75F, R78G, L80P, K81R, E82G, H88Y, F89L, R92G, S93G, S93R, L94A, D96G, A97T, L98S, K99G, K99R, L100P, E102G, Q103R, P104S, E105G, A107T, A107V, N108D, K109E, K109R, V110A, D111N, M112T, M112V, V113A, W114R, I115V, I115L, V116I, G117D, V121A, Y122C, Y122D, Y122I, K123R, K123E, A125F, M126I, N127R, N127S, N127Y, H128R, H128Y, H131R, L132P, K133E, L134P, F135P, F135L, F135S, F135V, V136M, T137R, R138G, R138I, I139T, I139V, M140I, M140V, Q141R, D142G, F143S, F143L, E144G, D146G, T147A, F148S, F148L, F149L, P150L, E151G, I152V, D153A, D153G, E155G, K156R, Y157R, Y157C, K158E, K158R, L159P, L160P, E162G, Y163C, V166A, S168C, D169G, V170A, Q171R, E172G, E173G, E173A, K174R, I176A, I176F, I176T, K177E, K177R, Y178C, Y178H, F180L, E181G, V182A, Y183C, Y183H, E184R, E184G, K185R, K185del, K185E, N186S, N186D, D187G, and D187N.

2. Payloads: Immunotherapeutic agents

[00154] In some embodiments, payloads of the present invention may be immunotherapeutic agents that induce immune responses in an organism. The immunotherapeutic agent may be, but is not limited to, an antibody and fragments and variants thereof, a chimeric antigen receptor

(CAR), a chimeric switch receptor, a cytokine, chemokine, a cytokine receptor, a chemokine receptor, a cytokine-cytokine receptor fusion polypeptide, or any agent that induces an immune response. In one embodiment, the immunotherapeutic agent induces an anti-cancer immune response in a cell, or in a subject.

Antibodies

[00155] In some embodiments, antibodies, fragments and variants thereof are payloads of the present invention.

[00156] In some embodiments, antibodies of the present invention, include without limitation, any of those taught in Table 5 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

Antibody fragments and variants

[00157] In some embodiments, antibody fragments and variants may comprise antigen binding regions from intact antibodies. Examples of antibody fragments and variants may include, but are not limited to Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules such as single chain variable fragment (scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site. Also produced is a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-binding sites and is still capable of cross-linking with the antigen. Pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention may comprise one or more of these fragments.

[00158] For the purposes herein, an "antibody" may comprise a heavy and light variable domain as well as an Fc region. As used herein, the term "native antibody" usually refers to a heterotetrameric glycoprotein of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda et al., *The Journal of Experimental Medicine*. 1998, 188(11): 2151-62 and Li et al., *Blood*, 2004, 103(12): 4602-4609; the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each

heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[00159] As used herein, the term "variable domain" refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. Variable domains comprise hypervariable regions. As used herein, the term "hypervariable region" refers to a region within a variable domain comprising amino acid residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody. As used herein, the term "CDR" refers to a region of an antibody comprising a structure that is complimentary to its target antigen or epitope. Other portions of the variable domain, not interacting with the antigen, are referred to as framework (FW) regions. The antigen-binding site (also known as the antigen combining site or paratope) comprises the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site are typically elucidated by co-crystallography with bound antigen, however computational assessments based on comparisons with other antibodies can also be used (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety). Determining residues that make up CDRs may include the use of numbering schemes including, but not limited to, those taught by Kabat (Wu et al., *JEM*, 1970, 132(2):211-250 and Johnson et al., *Nucleic Acids Res*. 2000, 28(1): 214-218, the contents of each of which are herein incorporated by reference in their entirety), Chothia (Chothia and Lesk, J. *Mol. Biol.* 1987, 196, 901, Chothia et al., *Nature,* 1989, 342, 877, and Al-Lazikani et al., *J. Mol. Biol*. 1997, 273(4): 927-948, the contents of each of which are herein incorporated by reference in their entirety), Lefranc (Lefranc et al., *Immunome Res*. 2005, 1:3) and Honegger (Honegger and Pluckthun, *J. Mol. Biol*. 2001, 309(3): 657-70, the contents of which are herein incorporated by reference in their entirety).

[00160] VH and VL domains have three CDRs each. VL CDRs are referred to herein as CDR-L1, CDR-L2 and CDR-L3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. VH CDRs are referred to herein as CDR-H1, CDR-H2 and CDR-H3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. Each of CDRs has favored canonical structures with the exception of the CDR-H3,

which comprises amino acid sequences that may be highly variable in sequence and length between antibodies resulting in a variety of three-dimensional structures in antigen-binding domains (Nikoloudis, et al., *PeerJ.* 2014, 2: e456). In some cases, CDR-H3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[00161] As used herein, the term "Fv" refers to an antibody fragment comprising the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable domain and the heavy chain variable domain (to form a single chain Fv (scFv)) or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[00162] As used herein, the term "light chain" refers to a component of an antibody from any vertebrate species assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes. There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

[00163] As used herein, the term "single chain Fv" or "scFv" refers to a fusion protein of VH and VL antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding. In some embodiments, scFvs are utilized in conjunction with phage display, yeast display or other display methods where they may be expressed in association with a surface member (e.g. phage coat protein) and used in the identification of high affinity peptides for a given antigen.

[00164] Using molecular genetics, two scFvs can be engineered in tandem into a single polypeptide, separated by a linker domain, called a "tandem scFv" (tascFv). Construction of a tascFv with genes for two different scFvs yields a "bispecific single-chain variable fragments" (bis-scFvs). Only two tascFvs have been developed clinically by commercial firms; both are

bispecific agents in active early phase development by Micromet for oncologic indications, and are described as "Bispecific T-cell Engagers (BiTE)." Blinatumomab is an anti-CD19/anti-CD3 bispecific tascFv that potentiates T-cell responses to B-cell non-Hodgkin lymphoma in Phase 2. MT110 is an anti-EP-CAM/anti-CD3 bispecific tascFv that potentiates T-cell responses to solid tumors in Phase 1. Bispecific, tetravalent "TandAbs" are also being researched by Affimed (Nelson, A. L., MAbs., 2010, Jan-Feb; 2(1):77–83). maxibodies (bivalent scFv fused to the amino terminus of the Fc (CH2-CH3 domains) of IgG may also be included.

[00165] As used herein, the term "bispecific antibody" refers to an antibody capable of binding two different antigens. Such antibodies typically comprise regions from at least two different antibodies. Bispecific antibodies may include any of those described in Riethmuller, G. *Cancer Immunity*. 2012, 12:12-18, Marvin et al., 2005. *Acta Pharmacologica Sinica*. 2005, 26(6): 649-658 and Schaefer et al., *PNAS*. 2011, 108(27):11187-11192, the contents of each of which are herein incorporated by reference in their entirety.

[00166] As used herein, the term "diabody" refers to a small antibody fragment with two antigen-binding sites. Diabodies are functional bispecific single-chain antibodies (bscAb). Diabodies comprise a heavy chain variable domain VH connected to a light chain variable domain VL in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al. (Hollinger, P. et al., "Diabodies": Small bivalent and bispecific antibody fragments. *PNAS*, 1993. 90: 6444-6448); the contents of each of which are incorporated herein by reference in their entirety.

[00167] The term "intrabody" refers to a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods of the present invention may include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein may be incorporated into one or more constructs for intrabody-based therapy.

[00168] As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous cells (or clones), i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibodies, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations that typically include

different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[00169] The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies herein include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[00170] As used herein, the term "humanized antibody" refers to a chimeric antibody comprising a minimal portion from one or more non-human (e.g., murine) antibody source(s) with the remainder derived from one or more human immunoglobulin sources. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from the hypervariable region from an antibody of the recipient are replaced by residues from the hypervariable region from an antibody of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and/or capacity. In one embodiment, the antibody may be a humanized full-length antibody. As a non-limiting example, the antibody may have been humanized using the methods taught in US Patent Publication NO. US20130303399, the contents of which are herein incorporated by reference in its entirety.

[00171] As used herein, the term "antibody variant" refers to a modified antibody (in relation to a native or starting antibody) or a biomolecule resembling a native or starting antibody in structure and/or function (e.g., an antibody mimetic). Antibody variants may be altered in their amino acid sequence, composition or structure as compared to a native antibody. Antibody variants may include, but are not limited to, antibodies with altered isotypes (e.g., IgA, IgD, IgE, IgG1, IgG2, IgG3, IgG4, or IgM), humanized variants, optimized variants, multispecific antibody variants (e.g., bispecific variants), and antibody fragments.

[00172] In some embodiments, pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention may be antibody mimetics. As used herein, the term "antibody mimetic" refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US

6,673,901; US 6,348,584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, Centyrins, DARPINSTM, Fynomers and Kunitz and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide regions.

[00173] In one embodiment, the antibody may comprise a modified Fc region. As a non-limiting example, the modified Fc region may be made by the methods or may be any of the regions described in US Patent Publication NO. US20150065690, the contents of which are herein incorporated by reference in its entirety.

[00174] In some embodiments, payloads of the invention may encode multispecific antibodies that bind more than one epitope. As used herein, the terms "multibody" or "multispecific antibody" refer to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In one embodiment, the multispecific antibody may be generated and optimized by the methods described in International Patent Publication NO. WO2011109726 and US Patent Publication NO. US20150252119, the contents of which each of which are herein incorporated by reference in their entirety. These antibodies are able to bind to multiple antigens with high specificity and high affinity.

[00175] In certain embodiments, a multi-specific antibody is a "bispecific antibody" which recognizes two different epitopes on the same or different antigens. In one aspect, bispecific antibodies are capable of binding two different antigens. Such antibodies typically comprise antigen-binding regions from at least two different antibodies. For example, a bispecific monoclonal antibody (BsMAb, BsAb) is an artificial protein composed of fragments of two different monoclonal antibodies, thus allowing the BsAb to bind to two different types of antigen. Bispecific antibody frameworks may include any of those described in Riethmuller, G., 2012. Cancer Immunity, 2012, 12:12-18; Marvin et al., Acta Pharmacologica Sinica. 2005, 26(6):649-658; and Schaefer et al., PNAS. 2011, 108(27): 11187-11192, the contents of each of which are herein incorporated by reference in their entirety. New generations of BsMAb, called "trifunctional bispecific" antibodies, have been developed. These consist of two heavy and two light chains, one each from two different antibodies, where the two Fab regions (the arms) are directed against two antigens, and the Fc region (the foot) comprises the two heavy chains and forms the third binding site.

[00176] In some embodiments, payloads may encode antibodies comprising a single antigen-binding domain. These molecules are extremely small, with molecular weights approximately one-tenth of those observed for full-sized mAbs. Further antibodies may include "nanobodies" derived from the antigen-binding variable heavy chain regions (VHHs) of heavy chain antibodies

found in camels and llamas, which lack light chains (Nelson, A. L., MAbs.2010. Jan-Feb; 2(1):77–83).

[00177] In some embodiments, the antibody may be "miniaturized". Among the best examples of mAb miniaturization are the small modular immunopharmaceuticals (SMIPs) from Trubion Pharmaceuticals. These molecules, which can be monovalent or bivalent, are recombinant single-chain molecules containing one VL, one VH antigen-binding domain, and one or two constant "effector" domains, all connected by linker domains. Presumably, such a molecule might offer the advantages of increased tissue or tumor penetration claimed by fragments while retaining the immune effector functions conferred by constant domains. At least three "miniaturized" SMIPs have entered clinical development. TRU-015, an anti-CD20 SMIP developed in collaboration with Wyeth, is the most advanced project, having progressed to Phase 2 for rheumatoid arthritis (RA). Earlier attempts in systemic lupus erythrematosus (SLE) and B cell lymphomas were ultimately discontinued. Trubion and Facet Biotechnology are collaborating in the development of TRU-016, an anti-CD37 SMIP, for the treatment of CLL and other lymphoid neoplasias, a project that has reached Phase 2. Wyeth has licensed the anti-CD20 SMIP SBI-087 for the treatment of autoimmune diseases, including RA, SLE and possibly multiple sclerosis, although these projects remain in the earliest stages of clinical testing. (Nelson, A. L., MAbs, 2010. Jan-Feb; 2(1):77–83).

[00178] On example of miniaturized antibodies is called "unibody" in which the hinge region has been removed from IgG4 molecules. While IgG4 molecules are unstable and can exchange light-heavy chain heterodimers with one another, deletion of the hinge region prevents heavy chain-heavy chain pairing entirely, leaving highly specific monovalent light/heavy heterodimers, while retaining the Fc region to ensure stability and half-life in vivo. This configuration may minimize the risk of immune activation or oncogenic growth, as IgG4 interacts poorly with FcRs and monovalent unibodies fail to promote intracellular signaling complex formation (see, e.g., Nelson, A. L., MAbs, 2010. Jan-Feb; 2(1):77–83).

[00179] In some embodiments, payloads of the invention may encode single-domain antibodies (sdAbs, or nanobodies) which are antibody fragment consisting of a single monomeric variable antibody domain. Like a whole antibody, it is able to bind selectively to a specific antigen. In one aspect, a sdAb may be a "Camel Ig or "camelid VHH". As used herein, the term "camel Ig" refers to the smallest known antigen-binding unit of a heavy chain antibody (Koch-No lte, et al, *FASEB J.*, 2007, 21: 3490- 3498). A "heavy chain antibody" or a "camelid antibody" refers to an antibody that contains two VH domains and no light chains (Riechmann L. et al, *J. Immunol. Methods*, 1999, 231: 25-38; International patent publication NOs. WO1994/04678 and

W01994/025591; and U.S. Patent No. 6,005,079). In another aspect, a sdAb may be a "immunoglobulin new antigen receptor" (IgNAR). As used herein, the term "immunoglobulin new antigen receptor" refers to class of antibodies from the shark immune repertoire that consist of homodimers of one variable new antigen receptor (VNAR) domain and five constant new antigen receptor (CNAR) domains. IgNARs represent some of the smallest known immunoglobulin-based protein scaffolds and are highly stable and possess efficient binding characteristics. The inherent stability can be attributed to both (i) the underlying Ig scaffold, which presents a considerable number of charged and hydrophilic surface exposed residues compared to the conventional antibody VH and VL domains found in murine antibodies; and (ii) stabilizing structural features in the complementary determining region (CDR) loops including inter-loop disulphide bridges, and patterns of intra-loop hydrogen bonds.

[00180] In some embodiments, payloads of the invention may encode intrabodies. Intrabodies are a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies are expressed and function intracellularly, and may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods described herein include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein are incorporated into one or more constructs for intrabody-based therapy. For example, intrabodies may target one or more glycated intracellular proteins or may modulate the interaction between one or more glycated intracellular proteins and an alternative protein.

[00181] The intracellular expression of intrabodies in different compartments of mammalian cells allows blocking or modulation of the function of endogenous molecules (Biocca, et al., *EMBO J.* 1990, 9: 101-108; Colby et al., *Proc. Natl. Acad. Sci. U.S.A.* 2004, 101: 17616-17621). Intrabodies can alter protein folding, protein-protein, protein-DNA, protein-RNA interactions and protein modification. They can induce a phenotypic knockout and work as neutralizing agents by direct binding to the target antigen, by diverting its intracellular trafficking or by inhibiting its association with binding partners. With high specificity and affinity to target antigens, intrabodies have advantages to block certain binding interactions of a particular target molecule, while sparing others.

[00182] Sequences from donor antibodies may be used to develop intrabodies. Intrabodies are often recombinantly expressed as single domain fragments such as isolated VH and VL domains or as a single chain variable fragment (scFv) antibody within the cell. For example, intrabodies are often expressed as a single polypeptide to form a single chain antibody comprising the

variable domains of the heavy and light chains joined by a flexible linker polypeptide. Intrabodies typically lack disulfide bonds and are capable of modulating the expression or activity of target genes through their specific binding activity. Single chain intrabodies are often expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (e.g., retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be produced using methods known in the art, such as those disclosed and reviewed in: (Marasco et al., *PNAS*, 1993, 90: 7889-7893; Chen et al., *Hum. Gene Ther.* 1994, 5:595-601; Chen et al., 1994, *PNAS*, 91: 5932-5936; Maciejewski et al., 1995, *Nature Med.*, 1: 667-673; Marasco, 1995, *Immunotech*, 1: 1-19; Mhashilkar, et al., 1995, *EMBO J.* 14: 1542-51; Chen et al., 1996, *Hum. Gene Therap.*, 7: 1515-1525; Marasco, *Gene Ther.* 4:11-15, 1997; Rondon and Marasco, 1997, Annu. Rev. Microbiol. 51:257-283; Cohen, et al., 1998, Oncogene 17:2445-56; Proba et al., 1998, J. Mol. Biol. 275:245-253; Cohen et al., 1998, Oncogene 17:2445-2456; Hassanzadeh, et al., 1998, FEBS Lett. 437:81-6; Richardson et al., 1998, Gene Ther. 5:635-44; Ohage and Steipe, 1999, J. Mol. Biol. 291:1119-1128; Ohage et al., 1999, J. Mol. Biol. 291:1129-1134; Wirtz and Steipe, 1999, Protein Sci. 8:2245-2250; Zhu et al., 1999, J. Immunol. Methods 231:207-222; Arafat et al., 2000, Cancer Gene Ther. 7:1250-6; der Maur et al., 2002, J. Biol. Chem. 277:45075-85; Mhashilkar et al., 2002, Gene Ther. 9:307-19; and Wheeler et al., 2003, FASEB J. 17: 1733-5; and references cited therein).

[00183] In some aspects, payloads of the invention may encode biosynthetic antibodies as described in U.S. Patent No. 5,091,513, the contents of which are herein incorporated by reference in their entirety. Such antibody may include one or more sequences of amino acids constituting a region which behaves as a biosynthetic antibody binding site (BABS). The sites comprise 1) non-covalently associated or disulfide bonded synthetic VH and VL dimers, 2) VH-VL or VL-VH single chains wherein the VH and VL are attached by a polypeptide linker, or 3) individuals VH or VL domains. The binding domains comprise linked CDR and FR regions, which may be derived from separate immunoglobulins. The biosynthetic antibodies may also include other polypeptide sequences which function, e.g., as an enzyme, toxin, binding site, or site of attachment to an immobilization media or radioactive atom. Methods are disclosed for producing the biosynthetic antibodies, for designing BABS having any specificity that can be elicited by in vivo generation of antibody, and for producing analogs thereof.

[00184] In some embodiments, payloads may encode antibodies with antibody acceptor frameworks taught in U.S. Patent No. 8,399,625. Such antibody acceptor frameworks may be particularly well suited accepting CDRs from an antibody of interest.

[00185] In one embodiment, the antibody may be a conditionally active biologic protein. An antibody may be used to generate a conditionally active biologic protein which are reversibly or irreversibly inactivated at the wild type normal physiological conditions as well as to such conditionally active biologic proteins and uses of such conditional active biologic proteins are provided. Such methods and conditionally active proteins are taught in, for example, International Publication No. WO2015175375 and WO2016036916 and US Patent Publication No. US20140378660, the contents of each of which are incorporated herein by reference in their entirety.

Antibody preparations

[00186] The preparation of antibodies, whether monoclonal or polyclonal, is known in the art. Techniques for the production of antibodies are well known in the art and described, e.g. in Harlow and Lane "Antibodies, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 1988; Harlow and Lane "Using Antibodies: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 1999 and "Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry" Woodhead Publishing, 2012.

[00187] The antibodies and fragments and variants thereof as described herein can be produced using recombinant polynucleotides. In one embodiment, the polynucleotides have a modular design to encode at least one of the antibodies, fragments or variants thereof. As a non-limiting example, the polynucleotide construct may encode any of the following designs: (1) the heavy chain of an antibody, (2) the light chain of an antibody, (3) the heavy and light chain of the antibody, (4) the heavy chain and light chain separated by a linker, (5) the VH1, CH1, CH2, CH3 domains, a linker and the light chain or (6) the VH1, CH1, CH2, CH3 domains, VL region, and the light chain. Any of these designs may also comprise optional linkers between any domain and/or region. The polynucleotides of the present invention may be engineered to produce any standard class of immunoglobulins using an antibody described herein or any of its component parts as a starting molecule.

[00188] Recombinant antibody fragments may also be isolated from phage antibody libraries using techniques well known in the art and described in e.g. Clackson et al., 1991, Nature 352: 624-628; Marks et al., 1991, J. Mol. Biol. 222: 581-597. Recombinant antibody fragments may be derived from large phage antibody libraries generated by recombination in bacteria (Sblattero and Bradbury, 2000, Nature Biotechnology 18:75-80; the contents of which are incorporated herein by reference in its entirety).

Antibodies used for immunotherapy

[00189] In some embodiments, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to tumor specific antigens (TSAs) and tumor associated antigens (TAAs). Antibodies circulate throughout the body until they find and attach to the TSA/TAA. Once attached, they recruit other parts of the immune system, increasing ADCC (antibody dependent cell-mediated cytotoxicity) and ADCP (antibody dependent cell-mediated phagocytosis) to destroy tumor cells. As used herein, the term "tumor specific antigen (TSA)" means an antigenic substance produced in tumor cells, which can trigger an anti-tumor immune response in a host organism. In one embodiment, a TSA may be a tumor neoantigen. The tumor antigen specific antibody mediates complement-dependent cytotoxic response against tumor cells expressing the same antigen.

[00190] In some embodiments, the tumor specific antigens (TSAs), tumor associated antigens (TAAs), pathogen associated antigens, or fragments thereof can be expressed as a peptide or as an intact protein or portion thereof. The intact protein or a portion thereof can be native or mutagenized. Antigens associated with cancers or virus-induced cancers as described herein are well-known in the art. Such a TSA or TAA may be previously associated with a cancer or may be identified by any method known in the art.

[00191] In one embodiment, the antigen is CD19, a B-cell surface protein expressed throughout B-cell development. CD19 is a well-known B cell surface molecule, which upon B cell receptor activation enhances B-cell antigen receptor induced signaling and expansion of B cell populations. CD19 is broadly expressed in both normal and neoplastic B cells. Malignancies derived from B cells such as chronic lymphocytic leukemia, acute lymphocytic leukemia and many non-Hodgkin lymphomas frequently retain CD19 expression. This near universal expression and specificity for a single cell lineage has made CD19 an attractive target for immunotherapies. Human CD19 has 14 exons wherein exon 1-4 encode the extracellular portion of the CD19, exon 5 encodes the transmembrane portion of CD19 and exons 6-14 encode the cytoplasmic tail.

[00192] In one embodiment, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to CD19 antigen.

[00193] In one embodiment, the payload of the invention may be a FMC63 antibody, antibody fragment of variant. FMC63 is an IgG2a mouse monoclonal antibody clone specific to the CD19 antigen that reacts with CD19 antigen on cells of the B cell lineage. The epitope of CD19 recognized by the FMC63 antibody is in exon 2 (Sotillo et al (2015) Cancer Discov ;5(12):1282-95; the contents of which are incorporated by reference in their entirety). In some embodiments,

the payload of the invention may be other CD19 monoclonal antibody clones including but not limited to 4G7, SJ25C1, CVID3/429, CVID3/155, HIB19, and J3-119.

[00194] In some embodiments, the payloads of the present invention may include variable heavy chain and variable light chain comprising the amino acid sequences selected from those in Table 4.

Table 4: Variable Heavy and Light Chain Sequences

Target	Antibody chain	SEQ ID NO	Source
CD19	VH	49	SEQ ID NO: 28 in WO2016168773A3
CD19	VH	50	SEQ ID NO: 29 in WO2016168773A3
CD19	VH	51	SEQ ID NO: 32 in WO2016168773A3
CD19	VH	52	SEQ ID NO: 33 in WO2016168773A3
CD19	VH	53	SEQ ID NO: 34 in WO2016168773A3
CD19	VH	54	SEQ ID NO: 35 in WO2016168773A3
CD19	VH	55	SEQ ID NO: 51 in WO2016187349A1
CD19	VH	56	SEQ ID NO: 20 in US20160039942
CD19	VH	57	SEQ ID NO. 1 in WO2014184143
CD19	VH	58	SEQ ID NO. 5 in US20160145337A1
CD19	VH	59	SEQ ID NO: 15 in US20160319020
CD19	VH	60	SEQ ID NO: 166 in US20160152723
CD19	VH	61	SEQ ID NO: 167 in US20160152723
CD19	VH	62	SEQ ID NO: 168 in US20160152723
CD19	VH	63	SEQ ID NO: 17 in EP3057991A1
CD19	VH	64	SEQ ID NO: 172 in US20160152723
CD19	VH	65	SEQ ID NO: 176 in US20160152723
CD19	VH	66	SEQ ID NO: 177 in US20160152723
CD19	VH	67	SEQ ID NO: 181 in US20160152723
CD19	VH	68	SEQ ID NO: 183 in US20160152723
CD19	VH	69	SEQ ID NO: 184 in US20160152723
CD19	VH	70	SEQ ID NO: 185 in US20160152723
CD19	VH	71	SEQ ID NO: 62 in US20160152723
CD19	VH	72	SEQ ID NO: 62 in WO2016097231
CD19	VH	73	SEQ ID NO. 12 in WO2016134284
CD19	VH	74	SEQ ID NO: 111 in US20160333114A1
CD19	VH	75	SEQ ID NO: 113 in US20160333114A1
CD19	VH	76	SEQ ID NO: 33 in EP3057994A1
CD19	VH	77	SEQ ID NO: 34 in EP3057994A1
CD19	VH	78	SEQ ID NO: 35 in EP3057994A1
CD19	VH	79	SEQ ID NO. 53 in WO2016120216
CD19	VH	80	SEQ ID NO. 55 in WO2016120216
CD19	VK	81	SEQ ID NO: 13 in US20160319020

CD19	VK	82	SEQ ID NO: 6 in US20160319020
CD19	VL	83	SEQ ID NO: 27 in WO2016168773A3
CD19	VL	84	SEQ ID NO: 31 in WO2016168773A3
CD19	VL	85	SEQ ID NO: 49 in WO2016187349A1
CD19	VL	86	SEQ ID NO. 11 in WO2016134284
CD19	VL	87	SEQ ID NO. 194 in US20140134142A1
CD19	VL	88	SEQ ID NO. 54 in WO2016120216
CD19	VL	89	SEQ ID NO. 56 in WO2016120216
CD19	VL	90	SEQ ID NO: 13 in US20160152723
CD19	VL	91	SEQ ID NO: 14 in US20160152723
CD19	VL	92	SEQ ID NO: 15 in US20160152723
CD19	VL	93	SEQ ID NO: 16 in US20160152723
CD19	VL	94	SEQ ID NO: 17 in US20160152723
CD19	VL	95	SEQ ID NO: 186 in US20160152723
CD19	VL	96	SEQ ID NO: 187 in US20160152723
CD19	VL	97	SEQ ID NO: 188 US20160152723
CD19	VL	98	SEQ ID NO: 189 in US20160152723
CD19	VL	99	SEQ ID NO: 192 in US20160152723
CD19	VL	100	SEQ ID NO: 196 in US20160152723
CD19	VL	101	SEQ ID NO: 197 in US20160152723
CD19	VL	102	SEQ ID NO: 198 in US20160152723
CD19	VL	103	SEQ ID NO: 199 in US20160152723
CD19	VL	104	SEQ ID NO: 200 in US20160152723
CD19	VL	105	SEQ ID NO: 201 in US20160152723
CD19	VL	106	SEQ ID NO: 202 in US20160152723
CD19	VL	107	SEQ ID NO: 203 in US20160152723
CD19	VL	108	SEQ ID NO: 204 in US20160152723
CD19	VL	109	SEQ ID NO: 205 in US20160152723
CD19	VL	110	SEQ ID NO: 22 in US20160039942
CD19	VL	111	SEQ ID NO: 63 in WO2016097231
CD19	VL	112	SEQ ID NO: 64 in US20160152723
CD19	VL	113	SEQ ID NO: 66 in US20160152723
CD19	VL	114	SEQ ID NO: 67 in US20160152723
CD19	VL	115	SEQ ID NO: 68 in US20160152723
CD19	VL	116	SEQ ID NO: 69 in US20160152723
CD19	VL	117	SEQ ID NO: 70 in US20160152723
CD19	VL	118	SEQ ID NO: 71 in US20160152723
CD19	VL	119	SEQ ID NO: 91 in US20160152723
CD19	VL	120	SEQ ID NO. 3 in US20160145337A1
CD19	VL	121	SEQ ID NO: 112 in US20160333114A1
CD19	VL	122	SEQ ID NO: 114 in US20160333114A1

[00195] A tumor specific antigen (TSA) may be a tumor neoantigen. A neoantigen is a mutated antigen that is only expressed by tumor cells because of genetic mutations or alterations in transcription which alter protein coding sequences, therefore creating novel, foreign antigens. The genetic changes result from genetic substitution, insertion, deletion or any other genetic changes of a native cognate protein (i.e. a molecule that is expressed in normal cells). In the context of CD19, neoantigens such as a transcript variant of CD19 lacking exon 2 or lacking exon 5-6 or both have been described (see International patent publication No. WO2016061368; the contents of which are incorporated herein by reference in their entirety). Since FMC63 binding epitope is in exon 2, CD19 neoantigen lacking exon 2 is not recognized by FMC63 antibody. Thus, in some embodiments, payloads of the invention may include FMC63-distinct antibodies, or fragments thereof. As used herein "FMC63-distinct" refers, to an antibody or fragment thereof that is immunologically specific and binds to an epitope of the CD19 antigen that is different or unlike the epitope of CD19 antigen that is bound by FMC63. In some instances, antibodies of the invention may include CD19 antibodies, antibody fragments or variants that recognize CD19 neoantigens including the CD19 neoantigen lacking exon2. In one embodiment, the antibody or fragment thereof is immunologically specific to the CD19 encoded by exon 1, 3 and/or 4. In one example, the antibody or fragment thereof is specific to the epitope that bridges the portion of CD19 encoded by exon 1 and the portion of CD19 encoded by exon 3.

[00196] Chimeric antigen receptors (CARs)

[00197] In some embodiments, payloads of the present invention may be a chimeric antigen receptors (CARs) which when transduced into immune cells (e.g., T cells and NK cells), can re-direct the immune cells against the target (e.g., a tumor cell) which expresses a molecule recognized by the extracellular target moiety of the CAR.

[00198] As used herein, the term "chimeric antigen receptor (CAR)" refers to a synthetic receptor that mimics TCR on the surface of T cells. In general, a CAR is composed of an extracellular targeting domain, a transmembrane domain/region and an intracellular signaling/activation domain. In a standard CAR receptor, the components: the extracellular targeting domain, transmembrane domain and intracellular signaling/activation domain, are linearly constructed as a single fusion protein. The extracellular region comprises a targeting domain/moiety (e.g., a scFv) that recognizes a specific tumor antigen or other tumor cell-surface molecules. The intracellular region may contain a signaling domain of TCR complex (e.g., the signal region of CD3ζ), and/or one or more costimulatory signaling domains, such as those from CD28, 4-1BB (CD137) and OX-40 (CD134). For example, a "first-generation CAR" only has the CD3ζ signaling domain. In an effort to augment T-cell persistence and proliferation,

costimulatory intracellular domains are added, giving rise to second generation CARs having a CD3ζsignal domain plus one costimulatory signaling domain, and third generation CARs having CD3ζ signal domain plus two or more costimulatory signaling domains. A CAR, when expressed by a T cell, endows the T cell with antigen specificity determined by the extracellular targeting moiety of the CAR. Recently, it is also desirable to add one or more elements such as homing and suicide genes to develop a more competent and safer architecture of CAR, so called the fourth-generation CAR.

[00199] In some embodiments, the extracellular targeting domain is joined through the hinge (also called space domain or spacer) and transmembrane regions to an intracellular signaling domain. The hinge connects the extracellular targeting domain to the transmembrane domain which transverses the cell membrane and connects to the intracellular signaling domain. The hinge may need to be varied to optimize the potency of CAR transformed cells toward cancer cells due to the size of the target protein where the targeting moiety binds, and the size and affinity of the targeting domain itself. Upon recognition and binding of the targeting moiety to the target cell, the intracellular signaling domain leads to an activation signal to the CAR T cell, which is further amplified by the "second signal" from one or more intracellular costimulatory domains. The CAR T cell, once activated, can destroy the target cell.

[00200] In some embodiments, the CAR of the present invention may be split into two parts, each part is linked a dimerizing domain, such that an input that triggers the dimerization promotes assembly of the intact functional receptor. Wu and Lim recently reported a split CAR in which the extracellular CD19 binding domain and the intracellular signaling element are separated and linked to the FKBP domain and the FRB* (T2089L mutant of FKBP-rapamycin binding) domain that heterodimerize in the presence of the rapamycin analog AP21967. The split receptor is assembled in the presence of AP21967 and together with the specific antigen binding, activates T cells (Wu et al., *Science*, 2015, 625(6258): aab4077).

[00201] In some embodiments, the CAR of the present invention may be designed as an inducible CAR. Sakemura et al recently reported the incorporation of a Tet-On inducible system to the CD19 CAR construct. The CD19 CAR is activated only in the presence of doxycycline (Dox). Sakemura reported that Tet-CD19CAR T cells in the presence of Dox were equivalently cytotoxic against $CD19^+$ cell lines and had equivalent cytokine production and proliferation upon CD19 stimulation, compared with conventional CD19CAR T cells (Sakemura et al., *Cancer Immuno. Res.*, 2016, Jun 21, Epub ahead of print). In one example, this Tet-CAR may be the payload of the effector module under the control of SREs (e.g., DDs) of the invention. The dual systems provide more flexibility to turn-on and off of the CAR expression in transduced T cells.

[00202] According to the present invention, the payload of the present invention may be a first-generation CAR, or a second-generation CAR, or a third-generation CAR, or a fourth-generation CAR. Representative effector module embodiments comprising CAR constructs are illustrated in Figures 13-18. In some embodiments, the payload of the present invention may be a full CAR construct composed of the extracellular domain, the hinge and transmembrane domain and the intracellular signaling region. In other embodiments, the payload of the present invention may be a component of the full CAR construct including an extracellular targeting moiety, a hinge region, a transmembrane domain, an intracellular signaling domain, one or more co-stimulatory domain, and other additional elements that improve CAR architecture and functionality including but not limited to a leader sequence, a homing element and a safety switch, or the combination of such components.

[00203] CARs regulated by biocircuits and compositions of the present invention are tunable and thereby offer several advantages. The reversible on-off switch mechanism allows management of acute toxicity caused by excessive CAR-T cell expansion. Pulsatile CAR expression using SREs of the present invention may be achieved by cycling ligand level. The ligand conferred regulation of the CAR may be effective in offsetting tumor escape induced by antigen loss, avoiding functional exhaustion caused by tonic signaling due to chronic antigen exposure and improving the persistence of CAR expressing cells *in vivo*.

[00204] In some embodiments, biocircuits and compositions of the invention may be utilized to down regulate CAR expression to limit on target on tissue toxicity caused by tumor lysis syndrome. Down regulating the expression of the CARs of the present invention following anti-tumor efficacy may prevent (1) On target off tumor toxicity caused by antigen expression in normal tissue, (2) antigen independent activation *in vivo*.

[00205] In one embodiment, selection of a CAR with a lower affinity may provide more T cell signaling and less toxicity.

Extracellular targeting domain/moiety

[00206] In accordance with the invention, the extracellular target moiety of a CAR may be any agent that recognizes and binds to a given target molecule, for example, a neoantigen on tumor cells, with high specificity and affinity. The target moiety may be an antibody and variants thereof that specifically binds to a target molecule on tumor cells, or a peptide aptamer selected from a random sequence pool based on its ability to bind to the target molecule on tumor cells, or a variant or fragment thereof that can bind to the target molecule on tumor cells, or an antigen recognition domain from native T- cell receptor (TCR) (e.g. CD4 extracellular domain to

recognize HIV infected cells), or exotic recognition components such as a linked cytokine that leads to recognition of target cells bearing the cytokine receptor, or a natural ligand of a receptor.

[00207] In some embodiments, the targeting domain of a CAR may be a Ig NAR, a Fab fragment, a Fab' fragment, a F(ab)'2 fragment, a F(ab)'3 fragment, Fv, a single chain variable fragment (scFv), a bis-scFv, a (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein (dsFv), a unitbody, a nanobody, or an antigen binding region derived from an antibody that specifically recognizes a target molecule, for example a tumor specific antigen (TSA). In one embodiment, the targeting moiety is a scFv antibody. The scFv domain, when it is expressed on the surface of a CAR T cell and subsequently binds to a target protein on a cancer cell, is able to maintain the CAR T cell in proximity to the cancer cell and to trigger the activation of the T cell. A scFv can be generated using routine recombinant DNA technology techniques and is discussed in the present invention.

[00208] In one embodiment, the targeting moiety of the CAR may recognize CD19. CD19 is a well-known B cell surface molecule, which upon B cell receptor activation enhances B-cell antigen receptor induced signaling and expansion of B cell populations. CD19 is broadly expressed in both normal and neoplastic B cells. Malignancies derived from B cells such as chronic lymphocytic leukemia, acute lymphocytic leukemia and many non-Hodgkin lymphomas frequently retain CD19 expression. This near universal expression and specificity for a single cell lineage has made CD19 an attractive target for immunotherapies. Human CD19 has 14 exons wherein exon 1-4 encode the extracellular portion of the CD19, exon 5 encodes the transmembrane portion of CD19 and exons 6-14 encode the cytoplasmic tail. In one embodiment, the targeting moiety may comprise scFvs derived from the variable regions of the FMC63 antibody. FMC63 is an IgG2a mouse monoclonal antibody clone specific to the CD19 antigen that reacts with CD19 antigen on cells of the B lineage. The epitope of CD19 recognized by the FMC63 antibody is in exon 2 (Sotillo et al (2015) Cancer Discov ;5(12):1282-95; the contents of which are incorporated by reference in their entirety). In some embodiments, the targeting moiety of the CAR may be derived from the variable regions of other CD19 monoclonal antibody clones including but not limited to 4G7, SJ25C1, CVID3/429, CVID3/155, HIB19, and J3-119.

[00209] In some embodiments, the targeting moiety of a CAR may recognize a tumor specific antigen (TSA), for example a cancer neoantigen that is only expressed by tumor cells because of genetic mutations or alterations in transcription which alter protein coding sequences, therefore creating novel, foreign antigens. The genetic changes result from genetic substitution, insertion, deletion or any other genetic changes of a native cognate protein (i.e. a molecule that is

expressed in normal cells). In the context of CD19, TSAs may include a transcript variant of human CD19 lacking exon 2 or lacking exon 5-6 or both (see International patent publication No. WO2016061368; the contents of which are incorporated herein by reference in their entirety). Since FMC63 binding epitope is in exon 2, CD19 lacking exon 2 is not recognized by FMC63 antibody. Thus, in some embodiments, the targeting moiety of the CAR may be an FMC63-distinct scFV. As used herein "FMC63-distinct" refers, to an antibody, scFv or a fragment thereof that is immunologically specific and binds to an epitope of the CD19 antigen that is different or unlike the epitope of CD19 antigen that is bound by FMC63. In some instances, targeting moiety may recognize a CD19 antigen lacking exon2. In one embodiment, the targeting moiety recognizes a fragment of CD19 encoded by exon 1, 3 and/or 4. In one example, the targeting moiety recognizes the epitope that bridges the portion of CD19 encoded by exon 1 and the portion of CD19 encoded by exon 3.

[00210] In some embodiments, the targeting moieties of the present invention may be scFv comprising the amino acid sequences in Table 5.

Table 5: scFv sequences

Target	Description	SEQ ID NO	Source
CD19	scFv	123	SEQ ID NO. 53 in EP3083671A1
CD19	scFv	124	SEQ ID NO. 54 in EP3083671A1
CD19	scFv	125	SEQ ID NO. 1 in WO2015157252
CD19	scFv	126	SEQ ID NO. 10 in WO2015157252
CD19	scFv	127	SEQ ID NO. 10 in WO2016033570
CD19	scFv	128	SEQ ID NO. 11 in WO2015157252
CD19	scFv	129	SEQ ID NO. 12 in WO2015157252
CD19	scFv	130	SEQ ID NO. 2 in WO2015157252
CD19	scFv	131	SEQ ID NO. 2 in WO2016033570
CD19	scFv	132	SEQ ID NO. 206 in WO2016033570
CD19	scFv	133	SEQ ID NO. 207 in WO2016033570
CD19	scFv	134	SEQ ID NO. 208 in WO2016033570
CD19	scFv	135	SEQ ID NO. 209 in WO2016033570
CD19	scFv	136	SEQ ID NO. 210 in WO2016033570
CD19	scFv	137	SEQ ID NO. 211 in WO2016033570
CD19	scFv	138	SEQ ID NO. 213 in WO2016033570
CD19	scFv	139	SEQ ID NO. 214 in WO2016033570
CD19	scFv	140	SEQ ID NO. 215 in WO2016033570
CD19	scFv	141	SEQ ID NO. 216 in WO2016033570
CD19	scFv	142	SEQ ID NO. 217 in WO2016033570
CD19	scFv	143	SEQ ID NO. 218 in WO2016033570
CD19	scFv	144	SEQ ID NO. 219 in WO2016033570
CD19	scFv	145	SEQ ID NO. 220 in WO2016033570
CD19	scFv	146	SEQ ID NO. 221 in WO2016033570
CD19	scFv	147	SEQ ID NO. 222 in WO2016033570
CD19	scFv	148	SEQ ID NO. 223 in WO2016033570
CD19	scFv	149	SEQ ID NO. 224 in WO2016033570
CD19	scFv	150	SEQ ID NO. 225 in WO2016033570
CD19	scFv	151	SEQ ID NO. 3 in WO2015157252
CD19	scFv	152	SEQ ID NO. 4 in WO2015157252

CD19	scFv	153	SEQ ID NO. 4 in WO2016033570
CD19	scFv	154	SEQ ID NO. 45 in WO2016033570
CD19	scFv	155	SEQ ID NO. 47 in WO2016033570
CD19	scFv	156	SEQ ID NO. 49 in WO2016033570
CD19	scFv	157	SEQ ID NO. 5 in WO2015155341A1
CD19	scFv	158	SEQ ID NO. 5 in WO2015157252
CD19	scFv	159	SEQ ID NO. 51 in WO2016033570
CD19	scFv	160	SEQ ID NO. 53 in WO2016033570
CD19	scFv	161	SEQ ID NO. 55 in WO2016033570
CD19	scFv	162	SEQ ID NO. 57 in WO2016033570
CD19	scFv	163	SEQ ID NO. 59 in WO2015157252
CD19	scFv	164	SEQ ID NO. 59 in WO2016033570
CD19	scFv	165	SEQ ID NO. 6 in WO2015157252
CD19	scFv	166	SEQ ID NO. 6 in WO2016033570
CD19	scFv	167	SEQ ID NO. 7 in WO2014184143
CD19	scFv	168	SEQ ID NO. 7 in WO2015157252
CD19	scFv	169	SEQ ID NO. 8 in WO2015157252
CD19	scFv	170	SEQ ID NO. 8 in WO2016033570
CD19	scFv	171	SEQ ID NO. 87 in WO2016033570
CD19	scFv	172	SEQ ID NO. 9 in WO2015157252
CD19	scFv	173	SEQ ID NO.9 in WO2016139487
CD19	scFv	174	SEQ ID NO. 10 in US20160152723
CD19	scFv	175	SEQ ID NO. 2 in US20160152723
CD19	scFv	176	SEQ ID NO. 206 in US20160152723
CD19	scFv	177	SEQ ID NO. 207 in US20160152723
CD19	scFv	178	SEQ ID NO. 208 in US20160152723
CD19	scFv	179	SEQ ID NO. 209 in US20160152723
CD19	scFv	180	SEQ ID NO. 210 in US20160152723
CD19	scFv	181	SEQ ID NO. 211 in US20160152723
CD19	scFv	182	SEQ ID NO. 212 in US20160152723
CD19	scFv	183	SEQ ID NO. 213 in US20160152723
CD19	scFv	184	SEQ ID NO. 214 in US20160152723
CD19	scFv	185	SEQ ID NO. 215 in US20160152723
CD19	scFv	186	SEQ ID NO. 216 in US20160152723
CD19	scFv	187	SEQ ID NO. 217 in US20160152723
CD19	scFv	188	SEQ ID NO. 218 in US20160152723
CD19	scFv	189	SEQ ID NO. 219 in US20160152723
CD19	scFv	190	SEQ ID NO. 220 in US20160152723
CD19	scFv	191	SEQ ID NO. 221 in US20160152723
CD19	scFv	192	SEQ ID NO. 222 in US20160152723
CD19	scFv	193	SEQ ID NO. 223 in US20160152723
CD19	scFv	194	SEQ ID NO. 224 in US20160152723
CD19	scFv	195	SEQ ID NO. 225 in US20160152723
CD19	scFv	196	SEQ ID NO. 32 in EP3083691A2
CD19	scFv	197	SEQ ID NO. 35 in EP3083691A2
CD19	scFv	198	SEQ ID NO. 38 in EP3083691A2
CD19	scFv	199	SEQ ID NO. 4 in US20160152723
CD19	scFv	200	SEQ ID NO. 45 in US20160152723
CD19	scFv	201	SEQ ID NO. 47 in US20160152723
CD19	scFv	202	SEQ ID NO. 49 in US20160152723
CD19	scFv	203	SEQ ID NO. 51 in US20160152723
CD19	scFv	204	SEQ ID NO. 53 in US20160152723
CD19	scFv	205	SEQ ID NO. 55 in US20160152723
CD19	scFv	206	SEQ ID NO. 57 in US20160152723
CD19	scFv	207	SEQ ID NO. 59 in US20160152723
CD19	scFv	208	SEQ ID NO. 6 in US20160152723
CD19	scFv	209	SEQ ID NO. 8 in US20160152723
CD19	scFv	210	SEQ ID NO. 87 in US20160152723

CD19	scFv	211	SEQ ID NO. 89 in US20160152723
CD19	scFv	212	SEQ ID NO. 39 in WO2016109410
CD19	scFv	213	SEQ ID NO. 37 in EP3083671A1
CD19	scFv	214	SEQ ID NO. 174 in WO2016115482
CD19	scFv	215	SEQ ID NO. 20 in WO2012079000
CD19	scFv	216	SEQ ID NO. 32 in WO2015092024
CD19	scFv	217	SEQ ID NO. 33 in WO2015092024A2
CD19	scFv	218	SEQ ID NO. 35 in WO2015092024A2
CD19	scFv	219	SEQ ID NO. 38 in WO2015092024A2
CD19	scFv	220	SEQ ID NO. 40 in WO2016109410
CD19	scFv	221	SEQ ID NO. 41 in WO2016109410
CD19	scFv	222	SEQ ID NO. 42 in WO2016109410
CD19	scFv	223	SEQ ID NO. 43 in WO2016109410
CD19	scFv	224	SEQ ID NO. 44 in WO2016109410
CD19	scFv	225	SEQ ID NO. 45 in WO2016109410
CD19	scFv	226	SEQ ID NO. 46 in WO2016109410
CD19	scFv	227	SEQ ID NO. 47 in WO2016109410
CD19	scFv	228	SEQ ID NO. 48 in WO2016109410
CD19	scFv	229	SEQ ID NO. 49 in WO2016109410
CD19	scFv	230	SEQ ID NO. 5 in WO2015155341A1
CD19	scFv	231	SEQ ID NO. 50 in WO2016109410
CD19	scFv	232	SEQ ID NO. 51 in WO2016109410
CD19	scFv	233	SEQ ID NO. 7 in US20160145337A1
CD19	scFv	234	SEQ ID NO. 9 in US20160145337A1
CD19	scFv	235	SEQ ID NO.20 in US9499629B2
CD19	scFv	236	SEQ ID NO.6 in WO2015155341A1
CD19	scFv	237	SEQ ID NO.73 in WO2016164580
CD19	scFv	238	SEQ ID NO. 10 US20160152723
CD19	scFv	239	SEQ ID NO. 2 in US20160152723
CD19	scFv	240	SEQ ID NO. 206 in US20160152723
CD19	scFv	241	SEQ ID NO. 207 in US20160152723
CD19	scFv	242	SEQ ID NO. 209 in US20160152723
CD19	scFv	243	SEQ ID NO. 210 in US20160152723
CD19	scFv	244	SEQ ID NO. 212 in US20160152723
CD19	scFv	245	SEQ ID NO. 216 in US20160152723
CD19	scFv	246	SEQ ID NO. 218 in US20160152723
CD19	scFv	247	SEQ ID NO. 219 in US20160152723
CD19	scFv	248	SEQ ID NO. 220 in US20160152723
CD19	scFv	249	SEQ ID NO. 221 in US20160152723
CD19	scFv	250	SEQ ID NO. 222 in US20160152723
CD19	scFv	251	SEQ ID NO. 223 in US20160152723
CD19	scFv	252	SEQ ID NO. 224 in US20160152723
CD19	scFv	253	SEQ ID NO. 225 in US20160152723
CD19	scFv	254	SEQ ID NO. 4 in US20160152723
CD19	scFv	255	SEQ ID NO. 45 in US20160152723
CD19	scFv	256	SEQ ID NO. 47 in US20160152723
CD19	scFv	257	SEQ ID NO. 49 in US20160152723
CD19	scFv	258	SEQ ID NO. 51 in US20160152723
CD19	scFv	259	SEQ ID NO. 53 in US20160152723
CD19	scFv	260	SEQ ID NO. 55 in US20160152723
CD19	scFv	261	SEQ ID NO. 57 in US20160152723
CD19	scFv	262	SEQ ID NO. 59 in US20160152723
CD19	scFv	263	SEQ ID NO. 6 in US20160152723
CD19	scFv	264	SEQ ID NO. 8 in US20160152723
CD19	scFv	265	SEQ ID NO. 87 in US20160152723
CD19	scFv	266	SEQ ID NO. 89 in US20160152723
CD19	scFv	267	SEQ ID NO. 5 in WO2016055551

Intracellular signaling domains

[00211] The intracellular domain of a CAR fusion polypeptide, after binding to its target molecule, transmits a signal to the immune effector cell, activating at least one of the normal effector functions of immune effector cells, including cytolytic activity (e.g., cytokine secretion) or helper activity. Therefore, the intracellular domain comprises an "intracellular signaling domain" of a T cell receptor (TCR).

[00212] In some aspects, the entire intracellular signaling domain can be employed. In other aspects, a truncated portion of the intracellular signaling domain may be used in place of the intact chain as long as it transduces the effector function signal.

[00213] In some embodiments, the intracellular signaling domain of the present invention may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs (ITAMs). Examples of ITAM containing cytoplasmic signaling sequences include those derived from TCR CD3zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d. In one example, the intracellular signaling domain is a CD3 zeta (CD3ζ) signaling domain.

[00214] In some embodiments, the intracellular region of the present invention further comprises one or more costimulatory signaling domains which provide additional signals to the immune effector cells. These costimulatory signaling domains, in combination with the signaling domain can further improve expansion, activation, memory, persistence, and tumor-eradicating efficiency of CAR engineered immune cells (e.g., CAR T cells). In some cases, the costimulatory signaling region contains 1, 2, 3, or 4 cytoplasmic domains of one or more intracellular signaling and /or costimulatory molecules. The costimulatory signaling domain may be the intracellular/cytoplasmic domain of a costimulatory molecule, including but not limited to CD2, CD7, CD27, CD28, 4-1BB (CD137), OX40 (CD134), CD30, CD40, ICOS (CD278), GITR (glucocorticoid-induced tumor necrosis factor receptor), LFA-1 (lymphocyte function-associated antigen- 1), LIGHT, NKG2C, B7-H3. In one example, the costimulatory signaling domain is derived from the cytoplasmic domain of CD28. In another example, the costimulatory signaling domain is derived from the cytoplasmic domain of 4-1BB (CD137). In another example, the co-stimulatory signaling domain may be an intracellular domain of GITR as taught in U.S. Pat. NO.: 9, 175, 308; the contents of which are incorporated herein by reference in its entirety.

[00215] In some embodiments, the intracellular region of the present invention may comprise a functional signaling domain from a protein selected from the group consisting of an MHC class I molecule, a TNF receptor protein, an immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation protein (SLAM) such as CD48, CD229, 2B4, CD84,

NTB-A, CRACC, BLAME,CD2F-10, SLAMF6, SLAMF7, an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, IL15Ra, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, NKD2C SLP76, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, CD270 (HVEM), GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, DAP 10, TRIM, ZAP70, Killer immunoglobulin receptors (KIRs) such as KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, and KIR2DP1; lectin related NK cell receptors such as Ly49, Ly49A, and Ly49C.

[00216] In some embodiments, the intracellular signaling domain of the present invention may contain signaling domains derived from JAK-STAT. In other embodiments, the intracellular signaling domain of the present invention may contain signaling domains derived from DAP-12 (Death associated protein 12) (Topfer et al., *Immunol.*, 2015, 194: 3201-3212; and Wang et al., Cancer Immunol., 2015, 3: 815-826). DAP-12 is a key signal transduction receptor in NK cells. The activating signals mediated by DAP-12 play important roles in triggering NK cell cytotoxicity responses toward certain tumor cells and virally infected cells. The cytoplasmic domain of DAP12 contains an Immunoreceptor Tyrosine-based Activation Motif (ITAM). Accordingly, a CAR containing a DAP12-derived signaling domain may be used for adoptive transfer of NK cells.

[00217] In some embodiments, T cells engineered with two or more CARs incorporating distinct co-stimulatory domains and regulated by distinct DD may be used to provide kinetic control of downstream signaling.

[00218] In some embodiments, the intracellular domain of the present invention may comprise amino acid sequences of Table 6.

Table 6: Intracellular signaling and co-stimulatory domains

Description	Amino Acid Sequence	Amino Acid SEQ ID
2B4 co-stimulatory domain	WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFP GGGSTIYSMIQSQSSAPTSQEPAYTLYSLIQPSRKSGSRKRN HSPSFNSTIYEVIGKSQPKAQNPARLSRKELENFDVYS	268
CD27 co-stimulatory domain	HQRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYR KPEPACSP	269
CD272 (BTLA1) co-stimulatory domain	RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQ VLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPGVYA SLNHSVIGPNSRLARNVKEAPTEYASICVRS	270
CD272 (BTLA1) co-stimulatory domain	CCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQ NSQVLLSETGIYDNDPDLCFRMQEGSEVYSNPCLEENKPG IVYASLNHSVIGPNSRLARNVKEAPTEYASICVRS	271
CD28 co-stimulatory	FWVLVVVGGVLACYSLLVTVAFIIFWV	272
CD28 co-stimulatory domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC EL	273
CD28 co-stimulatory domain	FWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDF AAYRS	274
CD28 co-stimulatory domain	RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RS	275
CD28 co-stimulatory domain	RSKRSRGGHSDYIVINMTPRRPGPTRKHYQPYAPPRDFAA YRS	276
CD28 co-stimulatory signaling region	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSC KYSYNLFSREFRASLHKGLDSAVEVCVVYGNYSQQLQVY SKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFCKIEVMYP PPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPG PTRKHYQPYAPPRDFAAYRS	277
CD30 co-stimulatory domain	RRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLR SGASVTEPVAEERGLMSQPLMETCHSVGAAYLESLPLQD ASPAGGPSSPRDLPEPRVSTEHTNNKIEKIYIMKADTVIVG TVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPPL GSCSDVMLSVEEEGKEDPLPTAASGK	278
CD30 co-stimulatory domain	RRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLR SGASVTEPVAEERGLMSQPLMETCHSVGAAYLESLPLQD ASPAGGPSSPRDLPEPRVSTEHTNNKIEKIYIMKADTVIVG TVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPPL GSCSDVMLSVEEEGKEDPLPTAASGK	279
GITR co-stimulatory domain	HIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGE RSAEEKGRLGDLWV	280
HVEM co-stimulatory domain	CVKRRKPRGDVVKVIVSVQRKRQEAEGEATVIEALQAPP DVTTVAVEETIPSFTGRSPNH	281
ICOS co-stimulatory domain	TKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL	282
ICOS co-stimulatory signaling domain	CWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL	283
LAG-3 co-stimulatory region	HLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPEP EPEPEPEPEPEQL	284
OX40 co-stimulatory domain	ALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLA KI	285
OX40 co-stimulatory domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	286
4-1BB intracellular domain	KRGRKKLLYIFKQPFMRPVQTIQEEDGCSCRFPEEEEGGCE L	287
4-1BB signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGY EL	288

4-1BB-CD3Zeta intracellular domain	TGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIF KQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDALHMQALPPR	289
4-1BB-Z endodomain fusion	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	290
CD127 intracellular domain	KRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLDC QIHRVDDIQARDEVEGFLQDTFPQQLEESEKQRLGGDVQS PNCPSEDVVITPESFGRDSSLTCLAGNVSACDAPILSSSRSL DCRESGKNGPHVYQDLLLSLGTTNSTLPPPFSLQSGILTLN PVAQGQPILTSLGSNQEEAYVTMSSFYQNQ	291
CD137 intracellular domain	RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCEL	292
CD148 intracellular domain	RKKRKDAKNNEVSFSQIKPKKSKLIRVENFEAYFKKQQAD SNCGFAEEYEDLKLVGISQPKYAAELAENRGKNRYNNVL PYDISRVKLSVQTHSTDDYINANYMPGYHSKKDFIATQGP LPNTLKDFWRMVWEKNVYAIIMLTKCVEQGRTKCEEYW PSKQAQDYGDITVAMTSEIVLPEWTIRDFTVKNIQTSESHP LRQFHFTSWPDHGVPDTTDLLINFRYLVRDYMKQSPPESPI LVHCSAGVGRTGTFIAIDRLIYQIENENTVDVYGIVYDLR MHRPLMVQTEDQYVFLNQCVLDIVRSQKDSKVDLIYQNT TAMTIYENLAPVTTFGKTNGYIA	293
CD27 intracellular domain	QRRKYRSNKGESPVEPAEPCHYSCPREEEGSTIPIQEDYRK PEPACSP	294
CD28 intracellular domain	FAAYRS	295
CD28 signaling chain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS	296
CD28 signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RS	297
CD28 signaling domain	SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR S	298
CD28 signaling domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFW VLVVVGGVLACYSLLVTVAFIIFWRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYAPPRDFAAYRS	299
CD28, 4-1BB, and/or CD3ζ signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP EEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR	300
CD28/CD3C	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSK PFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADA PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR	301
CD28-0XZ intracellular domain	RSKRSRLLHSDYNMTPRRPGPTRKHYQPYAPPRDFAAYRS RDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKIRVKFS RSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR	302
CD28-4-1BB intracellular domain	MFWVLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIF KQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	303

CD28-4-1BB intracellular domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFW VLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIFKQPF MRPVQTTQEEDGCSCRFPEEEEGGCEL	304
CD28-CD3 Zeta intracellular domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	305
CD28-CD3Zeta intracellular domain	KRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	306
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSIT WVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDK ESTVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLALGV FCFAGHETGRLSGAADTQALLRNDQVYQPLRDRDDAQYS HLGGNWARNK	307
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSIT WVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDK ESTVQVHYRTADTQALLRNDQVYQPLRDRDDAQYSHLG GNWARNK	308
CD3 delta chain intracellular signaling domain	DQVYQPLRDRDDAQYSHLGGN	309
CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSIT WVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDK ESTVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLALGV FCFAGHETGRLSGAADTQALLRNDQVYQPLRDRDDAQYS HLGGNWARNK	310
CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSIT WVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDK ESTVQVHYRTADTQALLRNDQVYQPLRDRDDAQYSHLG GNWARNK	311
CD3 delta intracellular domain	DQVYQPLRDRDDAQYSHLGGN	312
CD3 epsilon intracellular domain	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKV SISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDE DHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVC ENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAK AKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRD LYSGLNQRRI	313
CD3 epsilon intracellular domain	NPDYEPIRKGQRDLYSGLNQR	314
CD3 gamma intracellular domain	MEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQEDG SVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSNAK DPRGMYQCKGSQNKSKPLQVYYRMCQNCIELNAATISGF LFAEIVSIFVLAVGVYFIAGQDGVRQSRASDKQTLLPNDQ LYQPLKDREDDQYSHLQGNQLRRN,	315
CD3 gamma intracellular domain	DQLYQPLKDREDDQYSHLQGN	316
CD3 gamma intracellular domain	DQLYQPLKDREDDQYSHLQGN	317
CD3 gamma intracellular domain	MEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQEDG SVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSNAK DPRGMYQCKGSQNKSKPLQVYYRMCQNCIELNAATISGF LFAEIVSIFVLAVGVYFIAGQDGVRQSRASDKQTLLPNDQ LYQPLKDREDDQYSHLQGNQLRRN	318
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFI YGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM	319

	AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR	
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFI YGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	320
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFI YGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	321
CD3 zeta intracellular domain	NQLYNELNLGRREEYDVLDKR	322
CD3 zeta domain 2 (NM_000734.3)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	323
CD3 zeta intracellular domain	DGLYQGLSTATKDTYDALHMQ	324
CD3 zeta intracellular domain	RVKFSRSAEPPAYQQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	325
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	326
CD3 zeta intracellular domain	RSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	327
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR	328
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEVDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	329
CD3 zeta intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLVGIVLTL LVCRLKIQVRKAAITSYEKSRVKFSRSADAPAYQQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAVSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	330
CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	331
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPQRRKNPQEGLY	332
CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	333
CD3 zeta intracellular domain	RRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	334
CD3 zeta intracellular domain	NQLYNELNLGRREEYDVLDKR	335
CD3 zeta intracellular domain	EGLYNELQKDKMAEAYSEIGMK	336
CD3 zeta intracellular domain	DGLYQGLSTATKDTYDALHMQ	337
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	338

CD3 zeta intracellular domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	339
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALP	340
CD3 zeta intracellular domain	DPKLCYLLDGILFIYGVILTALFLRVKFSRSADAPAYQQGQ NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNP QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG LSTATKDTYDALHMQALPPR	341
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFI YGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR	342
CD40 intracellular domain	RSRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	343
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKVP ASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYTWP PEFLGPGEDPNGTLIIQNVNKSHGGIYVCRVQEGNESYQQ SCGTYLRVRQPPPRPFLDMGEGTKNRIITAEGIILLFCAVVP GTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLDDCS MYEDISRGLQGTYQDVGSLNIGDVQLEKP	344
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKVP ASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYTWP PEFLGPGEDPNEPPPRPFLDMGEGTKNRIITAEGIILLFCAV VPGTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLDDC SMYEDISRGLQGTYQDVGSLNIGDVQLEKP	345
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKVP ASLMVSLGEDAHFQCPHNSSNNANVTWWRVLHGNYTWP PEFLGPGEDPNGTLIIQNVNKSHGGIYVCRVQEGNESYQQ SCGTYLRVRQPPPRPFLDMGEGTKNRIITAEGIILLFCAVVP GTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLDDCS MYEDISRGLQGTYQDVGSLNIGDVQLEKP	346
CD79A intracellular domain	ENLYEGLNLDDCSMYEDISRG	347
CD8 intracellular domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHR NR	348
CD8 intracellular domain	FVPVFLPAKPITTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHR NR	349
CD8a intracellular domain	PTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDI	350
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVFVKMAPTEAECEKQFQPYFIPI N	351
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVYMNMTPRRPECEKQFQPYAPP RDFAAYRS	352
DAP10 intracellular domain	RPRRSPAQDGKVYINMPGRG	353
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEAAT RKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	354
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEATR KQRITETESPYQELQGQRSDVYSDLNTQRPYYK	355
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDL VLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESPY QELQGQRSDVYSDLNTQRPYYK	356

DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDL VLTVLIALAVYFLGRLVPRGRGAAEATRKQRITETESPYQ ELQGQRSDVYSDLNTQRPYYK	357
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEAAT RKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	358
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSP GVLAGIVMGDLVLTVLIALAVYFLGRLVPRGRGAAEATR KQRITETESPYQELQGQRSDVYSDLNTQRPYYK;	359
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDL VLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESPY QELQGQRSDVYSDLNTQRPYYK	360
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDL VLTVLIALAVYFLGRLVPRGRGAAEATRKQRITETESPYQ ELQGQRSDVYSDLNTQRPYYK	361
DAP12 intracellular domain	ESPYQELQGQRSDVYSDLNTQ	362
DAP12 intracellular domain	ESPYQELQGQRSDVYSDLNTQ	363
GITR intracellular domain	RSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEE KGRLGDLWV	364
ICOS intracellular domain	TKKKYSSSVHDPNGEFMFMRAVNTAKKSRLTDVTL	365
IL15Ra intracellular domain	KSRQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHL	366
OX40-CD3 Zeta intracellular domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKIRVK FSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	367
ZAP70 intracellular domain	MPDPAAHLPFFYGSISRAEAEEHLKLAGMADGLFLLRQCL RSLGGYVLSLVHDVRFHHFPIERQLNGTYAIAGGKAHCGP AELCEFYSRDPDGLPCNLRKPCNRPSGLEPQPGVFDCLRD AMVRDYVRQTWKLEGEALEQAIISQAPQVEKLIATTAHE RMPWYHSSLTREEAERKLYSGAQTDGKFLLRPRKEQGTY ALSLIYGKTVYHYLISQDKAGKYCIPEGTKFDTLWQLVEY LKLKADGLIYCLKEACPNSSASNASGAAAPTLPAHPSTLT HPQRRIDTLNSDGYTPEPARITSPDKPRPMPMDTSVYESPY SDPEELKDKKLFLKRDNLLIADIELGCGNFGSVRQGVYRM RKKQIDVAIKVLKQGTEKADTEEMMREAQIMHQLDNPYI VRLIGVCQAEALMLVMEMAGGGPLHKFLVGKREEIPVSN VAELLHQVSMGMKYLEEKNFVHRDLAARNVLLVNRHYA KISDFGLSKALGADDSYYTARSAGKWPLKWYAPECINFR KFSSRSDVWSYGVTMWEALSYGQKPYKKMKGPEVMAFI EQGKRMECPPECPPELYALMSDCWIYKWEDRPDFLTVEQ RMRACYYSLASKVEGPPGSTQKAEAACA	368
CD28 intracellular domain	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSC KYSYNLFSREFRASLHKGLDSAVEVCVVYGNYSQQLQVY SKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFCKIEVMYP PPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVG GVLACYSLLVTVAFIIFWVR	369
4-1BB intracellular domain	MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDNN RNQICSPCPPNSFSSAGGQRTCDICRQCKGVFRTRKECSST SNAECDCTPGFHCLGAGCSMCEQDCKQGQELTKKGCKD CCFGTFNDQKRGICRPWTNCSLDGKSVLVNGTKERDVVC GPSPADLSPGASSVTPPAPAREPGHSPQIISFFLALTSTALLF LLFFLTLRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDG	370
Fc epsilon Receptor I gamma chain intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLYGIVLTL LYCRLKIQVRKAAITSYEKSDGVYTGLSTRNQETYETLKH EKPPQ	371

Fc epsilon Receptor I gamma chain intracellular domain	DGVYTGLSTRNQETYETLKHE	372
Fc epsilon Receptor I gamma chain intracellular domain	DPKLCYILDAILFLYGIVLTLLYCRLKIQVRKAAITSYEKSD GVYTGLSTRNQETYETLKHEKPPQ	373
Fc epsilon Receptor I gamma chain intracellular domain	DGVYTGLSTRNQETYETLKHE	374

Transmembrane domains

[00219] In some embodiments, the CAR of the present invention may comprise a transmembrane domain. As used herein, the term "Transmembrane domain (TM)" refers broadly to an amino acid sequence of about 15 residues in length which spans the plasma membrane. More preferably, a transmembrane domain includes at least 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 amino acid residues and spans the plasma membrane. In some embodiments, the transmembrane domain of the present invention may be derived either from a natural or from a synthetic source. The transmembrane domain of a CAR may be derived from any naturally membrane-bound or transmembrane protein. For example, the transmembrane region may be derived from (i.e. comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T-cell receptor, CD3 epsilon, CD4, CD5, CD8, CD8α, CD9, CD16, CD22, CD33, CD28, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, or CD154.

[00220] Alternatively, the transmembrane domain of the present invention may be synthetic. In some aspects, the synthetic sequence may comprise predominantly hydrophobic residues such as leucine and valine.

[00221] In some embodiments, the transmembrane domain of the present invention may be selected from the group consisting of a CD8α transmembrane domain, a CD4 transmembrane domain, a CD 28 transmembrane domain, a CTLA-4 transmembrane domain, a PD-1 transmembrane domain, and a human Ig_{G4} Fc region. As non-limiting examples, the transmembrane domain may be a CTLA-4 transmembrane domain comprising the amino acid sequences of SEQ ID NOs.: 1-5 of International Patent Publication NO.: WO2014/100385; and a PD-1 transmembrane domain comprising the amino acid sequences of SEQ ID NOs.: 6-8 of International Patent Publication NO.: WO2014100385; the contents of each of which are incorporated herein by reference in their entirety.

[00222] In some embodiments, the CAR of the present invention may comprise an optional hinge region (also called spacer). A hinge sequence is a short sequence of amino acids that facilitates flexibility of the extracellular targeting domain that moves the target binding domain

away from the effector cell surface to enable proper cell/cell contact, target binding and effector cell activation (Patel et al., *Gene Therapy*, 1999; 6: 412-419). The hinge sequence may be positioned between the targeting moiety and the transmembrane domain. The hinge sequence can be any suitable sequence derived or obtained from any suitable molecule. The hinge sequence may be derived from all or part of an immunoglobulin (e.g., IgGl, IgG2, IgG3, IgG4) hinge region, i.e., the sequence that falls between the CHI and CH2 domains of an immunoglobulin, e.g., an IgG4 Fc hinge, the extracellular regions of type 1 membrane proteins such as CD8α CD4, CD28 and CD7, which may be a wild type sequence or a derivative. Some hinge regions include an immunoglobulin CH3 domain or both a CH3 domain and a CH2 domain. In certain embodiments, the hinge region may be modified from an IgG1, IgG2, IgG3, or IgG4 that includes one or more amino acid residues, for example, 1, 2, 3, 4 or 5 residues, substituted with an amino acid residue different from that present in an unmodified hinge. Table 7 provides various transmembrane regions that can be used in the CARs described herein.

Table 7: Transmembrane domains

Transmembrane domain	Amino Acid Sequence	SEQ ID NO.
CD8 Transmembrane domain	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDI	375
2B4 Transmembrane domain	FLVIIVILSALFLGTLACFCV	424
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVVKRGR	376
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVV	377
CD134 (OX40) Transmembrane domain	VAAILGLGLVLGLLGPLAILLALYLL	378
CD148 Transmembrane and intracellular domain	AVFGCIFGALVIVTVGGFIFWRKKRKDAKNNEVSFSQIKPK KSKLIRVENFEAYFKKQQADSNCGFAEEYEDLKLVGISQPK YAAELAENRGKNRYNNVLPYDISRVKLSVQTHSTDDYINA NYMPGYHSKKDFIATQGPLPNTLKDFWRMVWEKNVYAII MLTKCVEQGRTKCEEYWPSKQAQDYGDITVAMTSEIVLPE VVTIRDFTVKNIQTSESHPLRQFHFTSWPDHGVPDTTDLLIN FRYLVRDYMKQSPPESPILVHCSAGVGRTGTFIAIDRLIYQI ENENTVDVYGIVYDLRMHRPLMVQTEDQYVFLNQCVLDI VRSQKDSKVDLIYQNTTAMTIYENLAPVTTFGKTNGYIA	379
CD148 Transmembrane domain	AVFGCIFGALVIVTVGGFIFW	380
CD2 Transmembrane domain	KEITNALETWGALGQDINLDIPSFQMSDDIDDIKWEKTSDK KKIAQFRKEKETFKEKDTYKLFKNGTLKIKHLKTDDQDIYK VSIYDTKGKNVLEKIFDLKIQERVSKPKISWTCINTTLTCEV MNGTDPELNLYQDGKHLKLSQRVITHKWTTSLSAKFKCTA GNKVSKESSVEPVSCPEKGLD	381
CD28 Transmembrane and intracellular domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFW VLVVVGGVLACYSLLVTVAHIFWVRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYAPPRDFAAYRS	382
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWV	383
CD28 Transmembrane domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWV LVVVGGVLACYSLLVTVAFIIFWV	384

CD28 Transmembrane domain	IFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRR	385
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRS	386
CD28 Transmembrane domain	MFWVLVVVGGVLACYSLLVTVAFIIFWV	387
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFHFWV	388
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQAYAAARDFAAYRS	425
CD28 Transmembrane domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWV LWVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTP RRPGPTRKHYQPYAPPRDFAAYRS	897
CD28 Transmembrane domain	MFWVLVVVGGVLACYSGGVTVAFIIFWV	389
CD28 Transmembrane domain	WVLVVVGGVLACYSLLVTVAFIIFWV	390
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWVR	898
CD28 Transmembrane domain	PFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQPYAPPRDFAAYRS	391
CD28 Transmembrane domain and CD28 and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPA YQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR	392
CD28 Transmembrane domain and CD28, OX40, and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQPYAPPRDFAAYRSRDQRLPPDAHKP PGGGSFRTPIQEEQADAHSTLAKIRVKFSRSADAPAYQQGQ NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	393
CD28 Transmembrane domain and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRRVKFSRSADAPA YQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR	394
CD28 transmembrane-CD3 zeta signaling domain ("28z")	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPA YQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR	395
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFLRV	396
CD3 zeta Transmembrane domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIY GVILTALFL	397
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFL	398
CD4 Transmembrane domain	ALIVLGGVAGLLLFIGLGIFFCVRC	399
CD4 Transmembrane domain	MALIVLGGVAGLLLFIGLGIFF	400
CD45 Transmembrane and intracellular domain	ALIAFLAFLIIVTSIALLVVLYKIYDLHKKRSCNLDEQQELV ERDDEKQLMNVEPIHADILLETYKRKIADEGRLFLAEFQSIP RVFSKFPIKEARKPFNQNKNRYVDILPYDYNRVELSEINGD AGSNYINASYIDGFKEPRKYIAAQGPRDETVDDFWRMIWE QKATVIVMVTRCEEGNRNKCAEYWPSMEEGTRAFGDVVV KINQHKRCPDYIIQKLNIVNKKEKATGREVTHIQFTSWPDH GVPEDPHLLLKLRRRVNAFSNFFSGPIWHCSAGVGRTGTYI	401

	GIDAMLEGLEAENKVDVYGYVVKLRRQRCLMVQVEAQYI LIHQALVEYNQFGETEVNLSELHPYLHNMKKRDPPSEPSPL EAEFQRLPSYRSWRTQHIGNQEENKSKNRNSNVIPYDYNR VPLKHELEMSKESEHDSDESSDDDSDSEEPSKYINASFIMSY WKPEVMIAAQGPLKETIGDFWQMIFQRKVKVIVMLTELKH GDQEICAQYWGEGKQTYGDIEVDLKDTDKSSTYTLRVFEL RHSKRKDSRTVYQYQYTNWSVEQLPAEPKELISMIQWKQK LPQKNSSEGNKHHKSTPLLIHCRDGSQQTGIFCALLNLLES AETEEWDIFQWKALRKARPGMVSTFEQYQFLYDVIASTYP AQNGQVKKNNHQEDKIEFDNEVDKVKQDANCVNPLGAPE KLPEAKEQAEGSEPTSGTEGPEHSVNGPASPALNQGS	
CD62L Transmembrane domain	PLFIPVAVMVTAFSGLAFIIWLA	402
CD7 Transmembrane domain	ALPAALAVISFLLGLGLGVACVLA	403
CD8 Transmembrane domain	MALPVTALLLPLALLLHAARP	404
CD8 Transmembrane domain and CD28 signaling domain	AAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCN HRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFA AYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	405
CD8 transmembrane domain-CD137 (4-1BB) signaling domain and CD3 zeta signaling domain ("BBz")	AAATTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSAD APAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR	406
CD8a Transmembrane domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN	407
CD8a Transmembrane domain	IWAPLAGTCGVLLLSLVITLYC	408
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	409
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYCR	410
CD8a Transmembrane domain	PTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYCN	411
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLVCR	412
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVIT	413
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLY	414
CD8a Transmembrane domain (NP 001139345.1)	TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAWTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCNHRNRRR	899
CD8b Transmembrane domain	LGLLVAGVLVLLVSLGVAIHLCC	900
DAP10 Transmembrane domain	ILLAGLVAADAVASLLIVGAVFLCARR	901
EpoR Transmembrane domain	APVGLVARLADESGHVVLRWLPPPETPMTSHIRYEVDVSA GNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARMAE PSFGGFWSAWSEPVSLLTPSD	415
FcERI a Transmembrane domain	FFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRKGFRLLNP HPKPNPKNN	416

FcERI a- Transmembrane domain	MAPAMESPTLLCVALLFFAPDGVLAVPQKPKVSLNPPWNR IFKGENVTLTCNGNNFFEVSSTKWFHNGSLSEETNSSLNIV NAKFEDSGEYKCQHQQVNESEPVYLEVFSDWLLLQASAEV VMEGQPLFLRCHGWRNWDVYKVIYYKDGEALKYWYENH NISITNATVEDSGTYYCTGKVWQLDYESEPLNITVIKAPRE KYWLQFFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRKG FRLLNPHPKPNPKNN	417
FcERI b- Transmembrane region	MDTESNRRANLALPQEPSSVPAFEVLEISPQEVSSGRLLKSA SSPPLHTWLTVLKKEQEFLGVTQILTAMICLCFGTVVCSVL DISHIEGDIFSSFKAGYPFWGAIFFSISGMLSIISERRNATYLV RGSLGANTASSIAGGTGITILIINLKKSLAYIHIHSCQKFFETK CFMASFSTEIVVMMLFLTILGLGSAVSLTICGAGEELKGNK VPEDRVYEELNIYSATYSELEDPGEMSPPIDL	418
FcERI g- Transmembrane region	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLYGIVLTLL YCRLKIQVRKAAITSYEKSDGVYTGLSTRNQETYETLKHEK PPQ	419
FceRIa Transmembrane domain	DIFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRKGFRLLN PHPKPNPKNNR	420
GITR Transmembrane domain	PLGWLTVVLLAVAACVLLLTSAQLGLHIWQL	421
Her2 Transmembrane domain	SIISAVVGILLVVVLGVVFGILI	422
Her2 Transmembrane domain	CHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPS GVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGC PAEQRASPLTSIISAVVGILLVVVLGVVFGILI	423
ICOS Transmembrane domain	FWLPIGCAAFVVVCILGCILI	902
IgG1Transmembrane domain	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	903
LAG-3 Transmembrane domain	LLFLILGVLSLLLLVTGAFGF	904
OX40 Transmembrane domain	VAAILGLGLVLGLLGPLAILL	905
PD-1 Transmembrane domain	VGWGGLLGSLVLLVWVLAVI	906
Transmembrane domain	FWALVVVAGVLFCYGLLVTVALCVIWT	907

[00223] Hinge region sequences useful in the present invention are provided in Table 8A.

Table 8A: Hinge regions

Hinge Domain	**Amino Acid Sequence**	**SEQ ID NO.**
Hinge	DKTHT	426
Hinge	CPPC	427
Hinge	CPEPKSCDTPPPCPR	428
Hinge	ELKTPLGDTTHT	429
Hinge	KSCDKTHTCP	430
Hinge	KCCVDCP	431
Hinge	KYGPPCP	432
C233P Hinge	VEPKSPDKTHTCPPCP	433
C233S Hinge	LDPKSSDKTHTCPPCP	434

CD28 Hinge	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP	435
CD8a Hinge	GGAVHTRGLDFA	436
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	437
CD8a Hinge	AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACD	438
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	439
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACD	440
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDT	441
CD8a Hinge	PAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIY	442
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYC	443
CD8a Hinge	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACD	444
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIY	445
Delta5 Hinge	LDKTHTCPPCP	446
EpoR Hinge	APVGLVARLADESGHVVLRWLPPPETPMTSHIRYEVDVS AGNGAGSVQRVEILEGRTECVLSNLRGRTRYTFAVRARM AEPSFGGFWSAWSEPVSLLTPSD	447
FCRIIα Hinge	GLAVSTISSFFPPGYQ	448
FcγRIIIα Hinge	GLAVSTISSFFPPGYQ	449
Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	450
Hinge	YVTVSSQDPAEPKSPDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGKKDPK	451
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFA	452
Hinge	LEPKSCDKTHTCPPCP	453
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LD	454
Hinge	EPKSCDKTHTCPPCP	455
Hinge	ELKTPLGDTHTCPRCP	456
Hinge	EPKSCDTPPPCPRCP	457
Hinge	ESKYGPPCPSCP	458
Hinge	ERKCCVECPPCP	459
Hinge (CH2-CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA	460

	VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	
Hinge (CH3)	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	461
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	462
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLHPSL PPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCEV SGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSY VTDH	463
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMVVLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	464
IgD Hinge	ESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEE KKKEKEKEEQEERETKTP	465
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	466
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	467
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	468
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGR GGEEKKKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAV QDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPS LPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCE	469

	VSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFW AWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVS YVTDH	
IgG1 (CH2CH3) Hinge domain	AEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIART PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVUTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	470
IgG1 (CH2CH3) Hinge domain	AEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIART PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	471
IgG1 Hinge	AEPKSPDKTHTCPPCPKDPK	472
IgG1 Hinge	EPKSCDKTHTCPPCP	473
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEVKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	474
IgG1 Hinge	SVFLFPPKPKDTL	475
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	476
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKDPK	477
IgG1 Hinge	VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK	478
IgG1 Hinge (CH2CH3 domain)	DPAEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIA RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKK	479
IgG2 Hinge	ERKCCVECPPCP	480
IgG3 Hinge	ELKTPLGDTTHTCPRCP	481
IgG3 Hinge	ELKTPLGDTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPC PRCPEPKSCDTPPPCPRCP	482
IgG4 (CH2 and CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	483

IgG4 (CH2 and CH3)	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	484
IgG4 Hinge	SPNMVPHAHHAQ	485
IgG4 Hinge	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK	486
IgG4 Hinge	ESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	487
IgG4 Hinge	ESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHQAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFVPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	488
IgG4 Hinge	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHQAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFVPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	489
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	490
IgG4 Hinge	GAATCTAAGTACGGACCGCCCTGCCCCCCTTGCCCT	491
IgG4 Hinge	ESKYGPPCPPCP	492
IgG4 Hinge	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	493
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	494
IgG4 Hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	495
IgG4 Hinge	ESKYGPPCPPCP	496
IgG4 Hinge	YGPPCPPCP	497
IgG4 Hinge	KYGPPCPPCP	498
IgG4 Hinge	EVVKYGPPCPPCP	499
IgG4 Hinge	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA	500

	VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDLSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK	
IgG4 Hinge and Linker	ESKYGPPCPPCPGGGSSGGGSG	501
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTIPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	502
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTIPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	503
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	504

[00224] Hinge and transmembrane region sequences useful in the present invention are provided in Table 8B.

Table 8B: Hinge and Transmembrane regions

Hinge Domain	**Amino Acid Sequence**	**SEQ ID NO.**
CD8a Transmembrane and Hinge	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYC	505
CD8a Transmembrane and Hinge	DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQK PGNAPRLLISGATSLETGVPSRFSGSGSGKDYTLSITSLQTE DVATYYCQQYWSTPFTFGSGTKLEIKGGGGSGGGGSGGG GSQVQLKESGPGLVAPSQSLSITSTVSGFSLSRYSVHWVR QPPGKGLEWLGMIWGGGSTDYNSALKSRLSISKDNSKSQ VFLKMNSLQTDDTAMYYCARNEGDTTAGTWFAYWGQG TLVTVSS	506
CD8a Transmembrane and Hinge	ALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLS LRPEACRPAAGGAVHTRGLD	507
CD8a Transmembrane and Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLY	508
CD8a Transmembrane and Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLY	509

[00225] In some embodiments, the CAR of the present invention may comprise one or more linkers between any of the domains of the CAR. The linker may be between 1-30 amino acids long. In this regard, the linker may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acids in length. In other embodiments, the linker may be flexible.

[00226] In some embodiments, the components including the targeting moiety, transmembrane domain and intracellular signaling domains of the present invention may be constructed in a

single fusion polypeptide. The fusion polypeptide may be the payload of an effector module of the invention. In some embodiments, more than one CAR fusion polypeptides may be included in an effector module, for example, two, three or more CARs may be included in the effector module under the control of a single SRE (e.g., a DD). Representative effector modules comprising the CAR payload are illustrated in Figures 2-6.

[00227] In some embodiments, the CAR sequences may be selected from Table 9.

Table 9: CAR sequences

Description	SEQ ID NO	Source
CD19 CAR	510	SEQ ID NO: 12 in US9499629B2
CD19 CAR	511	SEQ ID NO: 24 in US20160333108A1
CD19 CAR	512	SEQ ID NO: 25 in US20160333108A1
CD19 CAR	513	SEQ ID NO: 26 in US20160333108A1
CD19 CAR	514	SEQ ID NO: 27 in US20160333108A1
CD19 CAR	515	SEQ ID NO: 1 in EP2997134A4
CD19 CAR	516	SEQ ID NO: 19 in EP3071687A1
CD19 CAR	517	SEQ ID NO: 20 in EP3071687A1
CD19 CAR	518	SEQ ID NO: 181 in WO2016168773A3
CD19 CAR	519	SEQ ID NO: 2 in WO2015157399A9
CD19 CAR	520	SEQ ID NO: 56 in WO2016174409A1
CD19 CAR	521	SEQ ID NO: 62 in WO2016174409A1
CD19 CAR	522	SEQ ID NO: 145 in WO2016179319A1
CD19 CAR	523	SEQ ID NO: 293 in US20160311907A1
CD19 CAR	524	SEQ ID NO: 294 in US20160311907A1
CD19 CAR	525	SEQ ID NO: 295 in US20160311907A1
CD19 CAR	526	SEQ ID NO: 296 in US20160311907A1
CD19 CAR	527	SEQ ID NO: 297 in US20160311907A1
CD19 CAR	528	SEQ ID NO: 298 in US20160311907A1
CD19 CAR	529	SEQ ID NO. 73 in WO2013176915A1
CD19 CAR	530	SEQ ID NO. 73 in WO2013176916A1
CD19 CAR	531	SEQ ID NO. 73 in US20130315884A1
CD19 CAR	532	SEQ ID NO. 73 in US20140134142A1
CD19 CAR	533	SEQ ID NO. 73 in US20150017136A1
CD19 CAR	534	SEQ ID NO. 73 in US20150203817A1
CD19 CAR	535	SEQ ID NO. 73 in US20160120905A1
CD19 CAR	536	SEQ ID NO. 73 in US20160120906A1
CD19 CAR	537	SEQ ID NO. 8 in WO2015124715
CD19 CAR	538	SEQ ID NO. 5 in WO2015124715
CD19 CAR	539	SEQ ID NO. 73 in WO2014184744
CD19 CAR	540	SEQ ID NO. 73 in WO2014184741
CD19 CAR	541	SEQ ID NO. 14 in US20160145337A1
CD19 CAR	542	SEQ ID NO. 15 in US20160145337A1
CD19 CAR	543	SEQ ID NO. 14 in WO2014184143
CD19 CAR	544	SEQ ID NO. 15 in WO2014184143
CD19 CAR	545	SEQ ID NO. 15 in WO2015075175
CD19 CAR	546	SEQ ID NO. 16 in WO2015075175
CD19 CAR	547	SEQ ID NO. 16 in US20160145337A1
CD19 CAR	548	SEQ ID NO. 16 in WO2014184143
CD19 CAR	549	SEQ ID NO 12 in WO2012079000
CD19 CAR	550	SEQ ID NO.31 in WO2016164580
CD19 CAR	551	SEQ ID NO.32 in WO2016164580
CD19 CAR	552	SEQ ID NO.33 in WO2016164580
CD19 CAR	553	SEQ ID NO.34 in WO2016164580

CD19 CAR	554	SEQ ID NO.35 in WO2016164580
CD19 CAR	555	SEQ ID NO.36 in WO2016164580
CD19 CAR	556	SEQ ID NO.37 in WO2016164580
CD19 CAR	557	SEQ ID NO.38 in WO2016164580
CD19 CAR	558	SEQ ID NO.39 in WO2016164580
CD19 CAR	559	SEQ ID NO.40 in WO2016164580
CD19 CAR	560	SEQ ID NO.41 in WO2016164580
CD19 CAR	561	SEQ ID NO.42 in WO2016164580
CD19 CAR	562	SEQ ID NO.58 in WO2016164580
CD19 CAR	563	SEQ ID NO: 14 in US20160296563A1
CD19 CAR	564	SEQ ID NO: 15 in US20160296563A1
CD19 CAR	565	SEQ ID NO.31 in WO2015157252
CD19 CAR	566	SEQ ID NO.32 in WO2015157252
CD19 CAR	567	SEQ ID NO.33 in WO2015157252
CD19 CAR	568	SEQ ID NO.34 in WO2015157252
CD19 CAR	569	SEQ ID NO.35 in WO2015157252
CD19 CAR	570	SEQ ID NO.36 in WO2015157252
CD19 CAR	571	SEQ ID NO.37 in WO2015157252
CD19 CAR	572	SEQ ID NO.38 in WO2015157252
CD19 CAR	573	SEQ ID NO.39 in WO2015157252
CD19 CAR	574	SEQ ID NO.40 in WO2015157252
CD19 CAR	575	SEQ ID NO.41 in WO2015157252
CD19 CAR	576	SEQ ID NO.42 in WO2015157252
CD19 CAR	577	SEQ ID NO. 14 in WO2016139487
CD19 CAR	578	SEQ ID NO.15 in WO2016139487
CD19 CAR	579	SEQ ID NO: 53 in US20160250258A1
CD19 CAR	580	SEQ ID NO: 54 in US20160250258A1
CD19 CAR	581	SEQ ID NO: 55 in US20160250258A1
CD19 CAR	582	SEQ ID NO: 56 in US20160250258A1
CD19 CAR	583	SEQ ID NO: 57 in US20160250258A1
CD19 CAR	584	SEQ ID NO: 58 in US20160250258A1
CD19 CAR	585	SEQ ID NO. 1 in WO2015187528
CD19 CAR	586	SEQ ID NO. 2 in WO2015187528
CD19 CAR	587	SEQ ID NO. 3 in WO2015187528
CD19 CAR	588	SEQ ID NO. 4 in WO2015187528
CD19 CAR	589	SEQ ID NO. 5 in WO2015187528
CD19 CAR	590	SEQ ID NO. 6 in WO2015187528
CD19 CAR	591	SEQ ID NO. 7 in WO2015187528
CD19 CAR	592	SEQ ID NO. 8 in WO2015187528
CD19 CAR	593	SEQ ID NO. 9 in WO2015187528
CD19 CAR	594	SEQ ID NO. 10 in WO2015187528
CD19 CAR	595	SEQ ID NO. 11 in WO2015187528
CD19 CAR	596	SEQ ID NO. 12 in WO2015187528
CD19 CAR	597	SEQ ID NO. 13 in WO2015187528
CD19 CAR	598	SEQ ID. NO. 31 in WO2015157252
CD19 CAR	599	SEQ ID. NO. 32 in WO2015157252
CD19 CAR	600	SEQ ID. NO. 33 in WO2015157252
CD19 CAR	601	SEQ ID. NO. 34 in WO2015157252
CD19 CAR	602	SEQ ID. NO. 35 in WO2015157252
CD19 CAR	603	SEQ ID. NO. 36 in WO2015157252
CD19 CAR	604	SEQ ID. NO. 37 in WO2015157252
CD19 CAR	605	SEQ ID. NO. 38 in WO2015157252
CD19 CAR	606	SEQ ID. NO. 39 in WO2015157252
CD19 CAR	607	SEQ ID. NO. 40 in WO2015157252
CD19 CAR	608	SEQ ID. NO. 41 in WO2015157252
CD19 CAR	609	SEQ ID. NO. 42 in WO2015157252
CD19 CAR	610	SEQ ID. NO. 58 in WO2015157252
CD19 CAR	611	SEQ ID NO. 31 in WO2014153270

CD19 CAR	612	SEQ ID NO. 32 in WO2014153270
CD19 CAR	613	SEQ ID NO. 33 in WO2014153270
CD19 CAR	614	SEQ ID NO. 34 in WO2014153270
CD19 CAR	615	SEQ ID NO. 35 in WO2014153270
CD19 CAR	616	SEQ ID NO. 36 in WO2014153270
CD19 CAR	617	SEQ ID NO. 37 in WO2014153270
CD19 CAR	618	SEQ ID NO. 38 in WO2014153270
CD19 CAR	619	SEQ ID NO. 39 in WO2014153270
CD19 CAR	620	SEQ ID NO. 40 in WO2014153270
CD19 CAR	621	SEQ ID NO. 41 in WO2014153270
CD19 CAR	622	SEQ ID NO. 42 in WO2014153270
CD19 CAR (Third generation)	623	SEQ ID NO.13 in WO2016139487

[00228] In one embodiment of the present invention, the payload of the invention is a CD19 specific CAR targeting different B cell. In the context of the invention, an effector module may comprise a hDHFR DD, ecDHFR DD, or FKBP DD operably linked to a CD19 CAR fusion construct. In some instances, the promoter utilized to drive the expression of the effector module in the vector may be a CMV promoter or an EF1a. The efficiency of the promoter in driving the expression of the same construct may be compared. For example, two constructs that differ only by their promoter, CMV (in OT-CD19N-001) or EF1a promoter (in OT-CD19N-017) may be compared. The amino acid sequences of CD19 CAR constructs and its components are presented in Table 10a and Table 10b. The amino acid sequences in Table 10a and/or Table 10b may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 10a: Sequences of components of CD19 CARs

Description	**Amino Acid Sequence**	**Amino Acid SEQ ID NO**	**Nucleic Acid SEQ ID NO**
CD19 scFv	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNW YQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTD YSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEI TGGGGSGGGGSGGGGSEVKLQESGPGLVAPSQSL SVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIW GSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQT DDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS S	624	626, 650-654
CD8α hinge--TM	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC	625	627, 655, 982-984
CD8α hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACD	440	656-660
CD3 zeta signaling domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	339	661-665, 986
4-1BB (41BB) intracellular signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCEL	273	666-670, 985
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	409	990, 992

CD8α leader	MALPVTALLLPLALLLHAARP	628	671-675
p40 signal sequence	MCHQQLVISWFSLVFLASPLVA	719	736-744
p40	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEE DGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEP KNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVK SSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSV ECQEDSACPAAEESLPIEVMVDAVHKLKYENYTS SFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDT WSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTS ATVICRKNASISVRAQDRYYSSSWSEWASVPCS	723	632-634, 752-761
p35	RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKA RQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELT KNESCLNSRETSFITNGSCLASRKTSFMMALCLSSI YEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNML AVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKL CILLHAFRIRAVTIDRVMSYLNAS	724	762-771, 1012
IL15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSC KVTAMKCFLLELQVISLESGDASIHDTVENLIILAN NSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIV QMFINTS	785	794-797, 1001
IL15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKR KAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL VHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPS SNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQGHSDTT VAISTSTVLLCGLSAVSLLACYLKSRQTPPLASVE MEAMEALPVTWGTSSRDEDLENCSHHL	803	812-813, 1003
mCherry (M1L)	LSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIE GEGEGRPYEGTQTAKLKVTKGGPLPFAWDILSPQ FMYGSKAYVKHPADIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPS DGPVMQKKTMGWEASSERMYPEDGALKGEIKQR LKLKDGGHYDAEVKTTYKAKKPVQLPGAYNVNI KLDITSHNEDYTIVEQYERAEGRHSTGGMDELYK	1029	1030
IRES	-	-	999
Linker (GGSGG)	GGSGG	629	676-680
Linker (SG)	SG	-	AGTGGA
Linker ((G4S)3)	GGGGSGGGGSGGGGS	720	910-915
Linker (GGSG)	GGSG	822	823
Linker	MLLLVTSLLLCELPHPAFLLIP	1031	1032
Linker (SG3-(SG4)3-SG3-SLQ)	SGGGSGGGGSGGGGSGGGGSGGGSLQ	802	811, 916-920, 1002
Modified Furin	ESRRVRRNKRSK	630	681-683
BamHI	-	-	GGATCC
Spacer	-	-	1000
HA Tag	YPYDVPDYA	1024	1025-1027
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGK KVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMS VGQRAKLTISPDYAYGATGHPGIIPPHATLVFDVE LLKPE	11	684-686, 987, 989
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDG KKVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQM SVGQGAKLTISPDYAYGATGHPGIIPPHATLVFDV ELLELE	12	688-691, 994, 1013, 1028
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRN TLNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDD RVTWVKSVDEAIAACGDVPEIMVIGGGRVIEQFLP	9	692, 772, 814, 687, 988, 991

	KAQKLYLTHIDAEVEGDTHFPDYEPDDWESVFSE FHDADAQNSHSYCFEILERR		
ecDHFR (Amino acid 2-159 of WT) (R12H, E129K)	ISLIAALAVDHVIGMENAMPWNLPADLAWFKRN TLNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDD RVTWVKSVDEAIAACGDVPEIMVIGGGRVYEQFL PKAQKLYLTHIDAEVEGDTHFPDYKPDDWESVFS EFHDADAQNSHSYCFEILERR	10	798, 815, 993
hDHFR (Amino acid 2-187 of WT; Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF QRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEAMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	895	694, 995
hDHFR (Amino acid 2-187 of WT; Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF QRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEFMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	890	696, 973, 974, 996
hDHFR (Amino acid 2-187 of WT; Q36K, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF KRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEAMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	981	698, 997
hDHFR (Q36F, N65F, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF FRMTTTSSVEGKQNLVIMGKKTWFSIPEKFRPLKG RINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPE LANKVDMVWIVGGSSVIKEAMNHPGHLKLFVTRI MQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQEEK GIKYKFEVYEKND	891	700, 975, 976, 998
Description	**Amino Acid Sequence**	**Amino Acid SEQ ID NO**	**Nucleic Acid SEQ ID NO**
CD19 scFv	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNW YQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTD YSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEI TGGGGSGGGGSGGGGSEVKLQESGPGLVAPSQSL SVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIW GSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQT DDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVS S	624	626, 650-654
CD8α hinge--TM	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC	625	627, 655, 982-984
CD8α hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACD	440	656-660
CD3 zeta signaling domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	339	661-665, 986
4-1BB (41BB) intracellular signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCEL	273	666-670, 985
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	409	990, 992
CD8α leader	MALPVTALLLPLALLLHAARP	628	671-675
p40 signal sequence	MCHQQLVISWFSLVFLASPLVA	719	736-744
p40	IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEE DGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEP	723	632-634, 752-761

	KNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVK SSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSV ECQEDSACPAAEESLPIEVMVDAVHKLKYENYTS SFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDT WSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTS ATVICRKNASISVRAQDRYYSSSWSEWASVPCS		
p35	RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKA RQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELT KNESCLNSRETSFITNGSCLASRKTSFMMALCLSSI YEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNML AVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKL CILLHAFRIRAVTIDRVMSYLNAS	724	762-771, 1012
IL15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSC KVTAMKCFLLELQVISLESGDASIHDTVENLIILAN NSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIV QMFINTS	785	794-797, 1001
IL15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKR KAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL VHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPS SNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQGHSDTT VAISTSTVLLCGLSAVSLLACYLKSRQTPPLASVE MEAMEALPVTWGTSSRDEDLENCSHHL	803	812-813, 1003
mCherry (M1L)	LSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIE GEGEGRPYEGTQTAKLKVTKGGPLPFAWDILSPQ FMYGSKAYVKHPADIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPS DGPVMQKKTMGWEASSERMYPEDGALKGEIKQR LKLKDGGHYDAEVKTTYKAKKPVQLPGAYNVNI KLDITSHNEDYTIVEQYERAEGRHSTGGMDELYK	1029	1030
IRES	-	-	999
Linker (GGSGG)	GGSGG	629	676-680
Linker (SG)	SG	-	AGTGGA
Linker ((G4S)3)	GGGGSGGGGSGGGGS	720	910-915
Linker (GGSG)	GGSG	822	823
Linker	MLLLVTSLLLCELPHPAFLLIP	1031	1032
Linker (SG3-(SG4)3-SG3-SLQ)	SGGGSGGGGSGGGGSGGGGSGGGSLQ	802	811, 916-920, 1002
Modified Furin	ESRRVRRNKRSK	630	681-683
BamHI	-	-	GGATCC
Spacer	-	-	1000
HA Tag	YPYDVPDYA	1024	1025-1027
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGK KVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMS VGQRAKLTISPDYAYGATGHPGIIPPHATLVFDVE LLKPE	11	684-686, 987, 989
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDG KKVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQM SVGQGAKLTISPDYAYGATGHPGIIPPHATLVFDV ELLELE	12	688-691, 994, 1013, 1028
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRN TLNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDD RVTWVKSVDEAIAACGDVPEIMVIGGGRVIEQFLP KAQKLYLTHIDAEVEGDTHFPDYEPDDWESVFSE FHDADAQNSHSYCFEILERR	9	692, 772, 814, 687, 988, 991
ecDHFR (Amino acid 2-159 of WT) (R12H, E129K)	ISLIAALAVDHVIGMENAMPWNLPADLAWFKRN TLNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDD RVTWVKSVDEAIAACGDVPEIMVIGGGRVYEQFL	10	798, 815, 993

	PKAQKLYLTHIDAEVEGDTHFPDYKPDDWESVFS EFHDADAQNSHSYCFEILERR		
hDHFR (Amino acid 2-187 of WT; Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF QRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEAMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	895	694, 995
hDHFR (Amino acid 2-187 of WT; Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF QRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEFMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	890	696, 973, 974, 996
hDHFR (Amino acid 2-187 of WT; Q36K, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF KRMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLK GRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQP ELANKVDMVWIVGGSSVIKEAMNHPGHLKLFVT RIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND	981	698, 997
hDHFR (Q36F, N65F, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYF FRMTTTSSVEGKQNLVIMGKKTWFSIPEKFRPLKG RINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPE LANKVDMVWIVGGSSVIKEAMNHPGHLKLFVTRI MQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQEEK GIKYKFEVYEKND	891	700, 975, 976, 998

Table 10b: Sequences of CD19 CARs

Description	Amino Acid Sequence	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO
OT-CD19 CAR-001 (OT-CD19c-001) (CD8a leader -CD19 scFV - CD8a-Tm -41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR*	635	701
OT-CD19 CAR-002 (OT-CD19c-002) (CD8a leader - CD19 scFV - FKBP (F36V, L106P) - CD8a-Tm - 41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSGVQVETISPGDG RTFPKRGQTCVVHYTGMLEDGKKVDSSRDRNKP FKFMLGKQEVIRGWEEGVAQMSVGQRAKLTISPD YAYGATGHPGIIPPHATLVFDVELLKPETTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA	636	702

	CDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLY IFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRV KFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR*		
OT-CD19 CAR-003 (OT-CD19c-003) (CD8a leader - CD19 scFV - ecDHFR - CD8a-Tm - 41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSISLIAALAVDYVI GMENAMPWNLPADLAWFKRNTLNKPVIMGRHT WESIGRPLPGRKNIILSSQPGTDDRVTWVKSVDEA IAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHID AEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHS YCFEILERRTTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR*	637	703
OT-CD19 CAR-004 (OT-CD19c-004) (CD8a leader - CD19 scFV - CD8a Hinge - FKBP (F36V, L106P) -CD8a Transmembrane domain-41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDGV QVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVG QRAKLTISPDYAYGATGHPGIIPPHATLVFDVELL KPEIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR VKFSRSADAPAYKQGQNQLYNELNLGRREEYDV LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR*	638	704
OT-CD19 CAR-005 (OT-CD19c-005) (CD8a leader - CD19 scFV - CD8a Hinge - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - CD8a Transmembrane domain -41BB -CD3zeta - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDISLI AALAVDYVIGMENAMPWNLPADLAWFKRNTLN KPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRV TWVKSVDEAIAACGDVPEIMVIGGGRVIEQFLPK AQKLYLTHIDAEVEGDTHFPDYEPDDWESVFSEF HDADAQNSHSYCFEILERRIYIWAPLAGTCGVLLL	639	705

	SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDALHMQALPPR*		
OT-CD19c-006 (CD8a leader-CD19 scFV - CD8a-Tm - 41BB - CD3zeta -linker (GGSGG) - ecDHFR (Amino acid 2-159 of WT) (R12H, E129K) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGISLIAALAVDHVIGMENAMPWNL PADLAWFKRNTLNKPVIMGRHTWESIGRPLPGRK NIILSSQPGTDDRVTWVKSVDEAIAACGDVPEIMV IGGGRVYEQFLPKAQKLYLTHIDAEVEGDTHFPD YKPDDWESVFSEFHDADAQNSHSYCFEILERR*	640	706
OT-CD19c-007 (CD8a leader - CD19 scFV- CD8a-Tm - 41BB - CD3zeta - linker (GGSGG) -FKBP (E31G, F36V, R71G, K105E) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGGVQVETISPGDGRTFPKRGQTCV VHYTGMLGDGKKVDSSRDRNKPFKFMLGKQEVI RGWEEGVAQMSVGQGAKLTISPDYAYGATGHPG IIPPHATLVFDVELLELE*	641	707
OT-CD19c-008 (CD8a leader - CD19 scFV - CD8a-Tm -41BB - CD3zeta - linker (GGSGG) - hDHFR (Amino acid 2-187 of WT; Y122I) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGVGSLNCIVAVSQNMGIGKNGDLP	642	708

	WPPLRNEFRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRS LDDALKLTEQPELANKVDMVWIVGGSSVIKEAM NHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLP EYPGVLSDVQEEKGIKYKFEVYEKND*		
OT-CD19c-009 (CD8a leader - CD19 scFV - CD8a-Tm - 41BB - CD3zeta -linker (GGSGG) - hDHFR (Amino acid 2-187 of WT; Y122I, A125F) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGVGSLNCIVAVSQNMGIGKNGDLP WPPLRNEFRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRS LDDALKLTEQPELANKVDMVWIVGGSSVIKEFM NHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLP EYPGVLSDVQEEKGIKYKFEVYEKND*	643	709
OT-CD19c-010 (CD8a leader - CD19 scFV - CD8a-Tm - 41BB - CD3zeta - linker (GGSGG) -hDHFR (Amino acid 2-187 of WT; Q36K, Y122I) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGVGSLNCIVAVSQNMGIGKNGDLP WPPLRNEFRYFKRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRS LDDALKLTEQPELANKVDMVWIVGGSSVIKEAM NHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLP EYPGVLSDVQEEKGIKYKFEVYEKND*	644	710
OT-CD19c-011 (CD8a leader -CD19 scFV - CD8a-Tm - 41BB - CD3zeta -linker (GGSGG) - hDHFR (Amino acid 2-187 of WT; Q36K,N65F, Y122I) -stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG	645	711

	RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGVGSLNCIVAVSQNMGIGKNGDLP WPPLRNEFRYFFRMTTTSSVEGKQNLVIMGKKTW FSIPEKFRPLKGRINLVLSRELKEPPQGAHFLSRSL DDALKLTEQPELANKVDMVWIVGGSSVIKEAMN HPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLPE YPGVLSDVQEEKGIKYKFEVYEKND*		
OT-CD19n-012 (CD8a leader - Linker (SG)-FKBP (F36V, L106P) - Furin Site -CD19 scFV - CD8a-Tm - 41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPSGGVQVETISPGDG RTFPKRGQTCVVHYTGMLEDGKKVDSSRDRNKP FKFMLGKQEVIRGWEEGVAQMSVGQRAKLTISPD YAYGATGHPGIIPPHATLVFDVELLKPEESRRVRR NKRSKDIQMTQTTSSLSASLGDRVTISCRASQDIS KYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSG SGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFG GGTKLEITGGGGSGGGGSGGGGSEVKLQESGPGL VAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLE WLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLK MNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQG TSVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLV ITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSC RFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYN ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR*	646	712
OT-CD19n-013 (CD8a leader - Linker (SG)-ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - Furin Site - CD19 scFV -CD8a-Tm - 41BB - CD3zeta - stop)	MALPVTALLLPLALLLHAARPSGISLIAALAVDYVI GMENAMPWNLPADLAWFKRNTLNKPVIMGRHT WESIGRPLPGRKNIILSSQPGTDDRVTWVKSVDEA IAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHID AEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHS YCFEILERRESRRVRRNKRSKDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR*	647	713
OT-CD19n-014 (CD8a leader - Linker (SG)-hDHFR (Amino acid 2-187 of WT, Y122I, A125F) - Furin Site - CD19 scFV - CD8a-Tm - 41BB -CD3zeta - stop)	MALPVTALLLPLALLLHAARPSGVGSLNCIVAVSQ NMGIGKNGDLPWPPLRNEFRYFQRMTTTSSVEGK QNLVIMGKKTWFSIPEKNRPLKGRINLVLSRELKE PPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEFMNHPGHLKLFVTRIMQDFESDTFFPEI DLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKN DESRRVRRNKRSKDIQMTQTTSSLSASLGDRVTIS CRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHS GVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVK LQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIR	648	714

	QPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDN SKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYA MDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLS LRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAY KQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR *		
OT-CD19n-015 (CD8a leader - Linker (SG)-hDHFR (Amino acid 2-187 of WT; Q36K, Y122I) -Furin Site - CD19 scFV - CD8a-Tm - 41BB - CD3zeta -stop)	MALPVTALLLPLALLLHAARPSGVGSLNCIVAVSQ NMGIGKNGDLPWPPLRNEFRYFKRMTTTSSVEGK QNLVIMGKKTWFSIPEKNRPLKGRINLVLSRELKE PPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPE IDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKN DESRRVRRNKRSKDIQMTQTTSSLSASLGDRVTIS CRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHS GVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQG NTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVK LQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIR QPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDN SKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYA MDYWGQGTSVTVSSTTTPAPRPPTPAPTIASQPLS LRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAY KQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR *	649	715
OT-CD19-056 (CD8a leader - CD19 scFV - CD8a-Tm - 41BB - CD3zeta - linker (GGSGG) - hDHFR (Amino acid 2-187 of WT; Y122I) -stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGGSGGVGSLNCIVAVSQNMGIGKNGDLP WPPLRNEFRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRS LDDALKLTEQPELANKVDMVWIVGGSSVIKEAM NHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLP EYPGVLSDVQEEKGIKYKFEVYEKND*	1005	1022
OT-CD19-057 (CD8a leader -CD19 scFV - CD8a-Tm - 41BB - CD3zeta - BamHI (GS)-stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS	1006	1023

	RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGS*		
OT-CD19-058 (CD8a leader -CD19 scFV - CD8a-Tm - 41BB - CD3zeta - p2A - BamHI (GS)- stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGATNFSLLKQAGDVEENPGPGS*	1007	1033
OT-CD19-059 (CD8a leader - HA Tag - CD19 scFV - CD8a-Tm - 41BB - CD3zeta - BamHI (GS)- stop)	MALPVTALLLPLALLLHAARPYPYDVPDYADIQM TQTTSSLSASLGDRVTISCRASQDISKYLNWYQQK PDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTI SNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGGG GSGGGGSGGGGSEVKLQESGPGLVAPSQSLSVTC TVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSET TYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTA IYYCAKHYYYGGSYAMDYWGQGTSVTVSSTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPRGS*	1008	1034
OT-CD19-060 (CD8a leader - CD19 scFV- CD8a-Tm- 41BB - CD3zeta - Linker (SG)- Furin - BamHI (GS)- stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRSGESRRVRRNKRSKGS*	1009	1035
OT-CD19-063 (CD8a leader - CD19 scFV -	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI	1010	1036

CD8a-Tm - 41BB - CD3zeta - stop)	YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR*		
OT-CD19-064 (CD8a leader - CD19 scFV - CD8a-Tm - 41BB - CD3zeta - Linker (TR)-HA Tag - FKBP (E31G, F36V, R71G, K105E) – stop-IRES- mCherry)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRTRYPYDVPDYAGVQVETISPGDGRTFPK RGQTCVVHYTGMLGDGKKVDSSRDRNKPFKFML GKQEVIRGWEEGVAQMSVGQGAKLTISPDYAYG ATGHPGIIPPHATLVFDVELLELE*MHRSAAAAT*I PPPPPLSLPPP*RYWPKPLGIRPVCVCLYVIFHHIAV FWQCEGPETWPCLLDEHS*GSFPSRQRNARSVEC REGSSSSGSFLKTNNVCSDPLQAAEPPTWRQVPLR PKATCIRYTCKGGTTPVPRCELDSCGKSQMALLK RIQQGAEGCPEGTPLYGI*SGASVHMLYMCLVEV KKTSRPPEPRGRGFPLKNTMIIWPQP**ARARRIT WPSSRSSCASRCTWRAP*TATSSRSRARARAAPTR APRPPS*R*PRVAPCPSPGTSCPLSSCTAPRPT*STP PTSPTT*SCPSPRASSGSA**TSRTAAW*P*PRTPPC RTASSSTR*SCAAPTSPPTAP*CRRRPWAGRPPPSG CTPRTAP*RARSSRG*S*RTAATTTLRSRPPTRPRS PCSCPAPTTSTSSWTSPPTTRTTPSWNSTNAPRAA TPPAAWTSCTS*	1215-1231	1037
OT-CD19-066 (CD8a leader - CD19 scFV - CD8a-Tm - 41BB - CD3zeta - Linker (GS)-P2A peptide -mCherry (M1L) - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM	1015	1039

	QALPPRGSGATNFSLLKQAGDVEENPGPLSKGEE DNMAIIKEFMRFKVHMEGSVNGHEFEIEGEGEGR PYEGTQTAKLKVTKGGPLPFAWDILSPQFMYGSK AYVKHPADIPDYLKLSFPEGFKWERVMNFEDGG VVTVTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQ KKTMGWEASSERMYPEDGALKGEIKQRLKLKDG GHYDAEVKTTYKAKKPVQLPGAYNVNIKLDITSH NEDYTIVEQYERAEGRHSTGGMDELYK*		
OT-CAR19-IL15-001 (CD8a leader - CD19 scFV -CD8a-Tm - 41BB - CD3zeta - Linker (GS)-P2A - IL15 -Linker (SG3-(SG4)3-SG3-SLQ) - IL15Ra - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGSGATNFSLLKQAGDVEENPGPNWVNVI SDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMK CFLLELQVISLESGDASIHDTVENLIILANNSLSSNG NVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS SGGGSGGGGSGGGGSGGGGSGGGSLQITCPPPMS VEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT ECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPP STVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATT AAIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTT AKNWELTASASHQPPGVYPQGHSDTTVAISTSTV LLCGLSAVSLLACYLKSRQTPPLASVEMEAMEAL PVTWGTSSRDEDLENCSHHL*	1016	1040
OT-CAR19-IL15-002 (CD8a leader -CD19 scFV -CD8a-Tm -41BB - CD3zeta - Linker (GS)-P2A - Linker (MLLLVTSLLLCELPHP AFLLIP) (SEQ ID NO: 1031) - IL15 - Linker (SG3-(SG4)3-SG3-SLQ) - IL15Ra - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGSGATNFSLLKQAGDVEENPGPMLLLVT SLLLCELPHPAFLLIPNWVNVISDLKKIEDLIQSMH IDATLYTESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTVENLIILANNSLSSNGNVTESGCKECEEL EEKNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADIWVKSYS LYSRERYICNSGFKRKAGTSSLTECVLNKATNVA HWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQP ESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPS KSPSTGTTEISSHESSHGTPSQTTAKNWELTASAS	1017	1041

	HQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWGTSSRDED LENCSHHL*		
OT-CD19-IL15-006 (CD8a leader -CD19 scFV - CD8a-Tm - 41BB - CD3zeta - Linker (GS)-P2A - IgE Leader - IL15 - Linker (SG3-(SG4)3-SG3-SLQ) - IL15Ra - stop)	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSAS LGDRVTISCRASQDISKYLNWYQQKPDGTVKLLI YHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIA TYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSG GGGSEVKLQESGPGLVAPSQSLSVTCTVSGVSLPD YGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKS RLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHY YYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRGSGATNFSLLKQAGDVEENPGPMDWTW ILFLVAAATRVHSNWVNVISDLKKIEDLIQSMHID ATLYTESDVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCKECEELEE KNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGGGG SGGGGSGGGSLQITCPPPMSVEHADIWVKSYSLYS RERYICNSGFKRKAGTSSLTECVLNKATNVAHWT TPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLS PSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPS TGTTEISSHESSHGTPSQTTAKNWELTASASHQPP GVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLK SRQTPPLASVEMEAMEALPVTWGTSSRDEDLENC SHHL*	1018	1042

[00229] Constructs disclosed in Table 10 which are transcriptionally controlled by a CMV promoter, in some instances may be placed under the transcriptional control of a different promoter to test the role of promoters in CD19 CAR expression. In one embodiment, the CMV promoter may be replaced by an EF1a promoter. In one embodiment, the CMV promoter of the, OT-CD19-001 construct, may be replaced to generate OT-CD19N-017 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-002 construct, may be replaced to generate OT-CD19N-018 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-003 construct, may be replaced to generate OT-CD19N-019 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-004 construct, may be replaced to generate OT-CD19N-020 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-005 construct, may be replaced to generate OT-CD19N-021 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-006 construct, may be replaced to generate OT-CD19N-022 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the

CD19 CAR, OT-CD19 CAR-007 construct, may be replaced to generate OT-CD19N-023 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-008 construct, may be replaced to generate OT-CD19N-024 construct, with a EF1a promoter. In another embodiment, the CMV promoter of the CD19 CAR, OT-CD19 CAR-009 construct, may be replaced to generate OT-CD19N-025 construct, with a EF1a promoter.

[00230] In one embodiment, the CAR construct comprises a CD19 scFV (e.g., CAT13.1E10 or FMC63), a CD8α spacer or transmembrane domain, and a 4-1BB and CD3ζ endodomain. These constructs with CAT13.1E10 may have increased proliferation after stimulation *in vitro*, increased cytotoxicity against the CD19+ targets, and increased effector and target interactions as compared to constructs with FMC63.

[00231] In some embodiments, the payloads of the present invention may be tuned using the catalytic domains of the E3 ubiquitin ligases. The catalytic domains of E3 ligases may be fused to an antibody or a fragment of the antibody. The payload is fused to the antigen recognized by the antibody or a fragment of the antibody that is fused to the E3 ligases catalytic domain. The E3 ligases useful in the present invention include, but are not limited to Ring E3 ligase, HECT E3 ligases and RBR E3 ligases. Any of the methods taught by Kanner SA et al. (2017) eLife; 6: e29744 may be useful in the present invention (the contents of which are incorporated by reference in their entirety).

[00232] In some embodiments, the payloads described herein, may be regulated by E3 ubiquitin ligases constructs. The E3 ligases constructs may comprise the catalytic domain of E3 ligases fused to an SRE and an antibody or a fragment of an antibody. The payloads are fused to the antigen recognized by the antibody or a fragment of an antibody, that is appended to the catalytic domain of E3 ligases. In the absence of the stimulus corresponding to the SRE, the E3 ubiquitin ligases constructs are destabilized, which in turn, allows the expression of the payloads fused to the antigen. In the presence of ligand corresponding to the SRE, the E3 ubiquitin ligases constructs are stabilized and available to bind to the antigen fused to the payloads. Binding of the E3 ligases constructs to the antigens, targets the protein for degradation. The E3 ubiquitin ligases constructs may be used to regulate any payload described herein, provided the payload is fused to an antigen recognized by the antibody or the fragment of the antibody in the E3 ubiquitin ligases construct. In some embodiments, the payload is a chimeric antigen receptor. The E3 ubiquitin ligases constructs may be used to design logic gates. In one embodiment, the E3 ubiquitin ligases constructs may be used to generate a NOT gate, wherein one ligand induces the expression of the payload, while another inhibits the expression of the payload. In some embodiments, the NOT gate may be generated using the E3 ubiquitin ligases constructs and by

fusing the payloads-antigen fusion protein to a second a SRE that is distinct from the SRE in the E3 ubiquitin ligase construct.

[00233] In some embodiments, the payload of the invention may be any of the co-stimulatory molecules and/or intracellular domains described herein. In some embodiments, one or more co-stimulatory molecules, each under the control of different SRE may be used in the present invention. SRE regulated co- stimulatory molecules may also be expressed in conjunction with a first generation CAR, a second generation CAR, a third generation CAR, a fourth generation, or any other CAR design described herein.

Tandem CAR (TanCAR)

[00234] In some embodiments, the CAR of the present invention may be a tandem chimeric antigen receptor (TanCAR) which is able to target two, three, four, or more tumor specific antigens. In some aspects, The CAR is a bispecific TanCAR including two targeting domains which recognize two different TSAs on tumor cells. The bispecific CAR may be further defined as comprising an extracellular region comprising a targeting domain (e.g., an antigen recognition domain) specific for a first tumor antigen and a targeting domain (e.g., an antigen recognition domain) specific for a second tumor antigen. In other aspects, the CAR is a multispecific TanCAR that includes three or more targeting domains configured in a tandem arrangement. The space between the targeting domains in the TanCAR may be between about 5 and about 30 amino acids in length, for example, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 amino acids.

Split CAR

[00235] In some embodiments, the components including the targeting moiety, transmembrane domain and intracellular signaling domains of the present invention may be split into two or more parts such that it is dependent on multiple inputs that promote assembly of the intact functional receptor. In one embodiment, the split synthetic CAR system can be constructed in which the assembly of an activated CAR receptor is dependent on the binding of a ligand to the SRE (e.g. a small molecule) and a specific antigen to the targeting moiety. As a non-limiting example, the split CAR consists of two parts that assemble in a small molecule-dependent manner; one part of the receptor features an extracellular antigen binding domain (e.g. scFv) and the other part has the intracellular signaling domains, such as the CD3ζ intracellular domain.

[00236] In other aspects, the split parts of the CAR system can be further modified to increase signal. In one example, the second part of cytoplasmic fragment may be anchored to the plasma membrane by incorporating a transmembrane domain (e.g., CD8α transmembrane domain) to the construct. An additional extracellular domain may also be added to the second part of the CAR

system, for instance an extracellular domain that mediates homo-dimerization. These modifications may increase receptor output activity, i.e., T cell activation.

[00237] In some aspects, the two parts of the split CAR system contain heterodimerization domains that conditionally interact upon binding of a heterodimerizing small molecule. As such, the receptor components are assembled in the presence of the small molecule, to form an intact system which can then be activated by antigen engagement. Any known heterodimerizing components can be incorporated into a split CAR system. Other small molecule dependent heterodimerization domains may also be used, including, but not limited to, gibberellin-induced dimerization system (GID1-GAI), trimethoprim-SLF induced ecDHFR and FKBP dimerization (Czlapinski et al., *J Am Chem Soc.*, 2008, 130(40): 13186-13187) and ABA (abscisic acid) induced dimerization of PP2C and PYL domains (Cutler et al., *Annu Rev Plant Biol.* 2010, 61: 651-679). The dual regulation using inducible assembly (e.g., ligand dependent dimerization) and degradation (e.g., destabilizing domain induced CAR degradation) of the split CAR system may provide more flexibility to control the activity of the CAR modified T cells.

Switchable CAR

[00238] In some embodiments, the CAR of the invention may be a switchable CAR. Juillerat et al (Juilerat et al., *Sci. Rep.*, 2016, 6: 18950; the contents of which are incorporated herein by reference in their entirety) recently reported controllable CARs that can be transiently switched on in response to a stimulus (e.g. a small molecule). In this CAR design, a system is directly integrated in the hinge domain that separate the scFv domain from the cell membrane domain in the CAR. Such system is possible to split or combine different key functions of a CAR such as activation and costimulation within different chains of a receptor complex, mimicking the complexity of the TCR native architecture. This integrated system can switch the scFv and antigen interaction between on/off states controlled by the absence/presence of the stimulus.

Reversible CAR

[00239] In other embodiments, the CAR of the invention may be a reversible CAR system. In this CAR architecture, a LID domain (ligand-induced degradation) is incorporated into the CAR system. The CAR can be temporarily down-regulated by adding a ligand of the LID domain. The combination of LID and DD mediated regulation provides tunable control of continuingly activated CAR T cells, thereby reducing CAR mediated tissue toxicity.

Activation-conditional CAR

[00240] In some embodiments, payloads of the invention may be an activation-conditional chimeric antigen receptor, which is only expressed in an activated immune cell. The expression of the CAR may be coupled to activation conditional control region which refers to one or more

nucleic acid sequences that induce the transcription and/or expression of a sequence e.g. a CAR under its control. Such activation conditional control regions may be promoters of genes that are upregulated during the activation of the immune effector cell e.g. IL2 promoter or NFAT binding sites. In some embodiments, activation of the immune cell may be achieved by a constitutively expressed CAR (International Publication No: WO2016126608; the contents of which are incorporated herein by reference in their entirety).

Cytokines, chemokines and other soluble factors

[00241] In accordance with the present invention, CARs of the present invention may be utilized along with other payloads of the present invention may be cytokines, chemokines, growth factors, and soluble proteins produced by immune cells, cancer cells and other cell types, which act as chemical communicators between cells and tissues within the body. These proteins mediate a wide range of physiological functions, from effects on cell growth, differentiation, migration and survival, to a number of effector activities. For example, activated T cells produce a variety of cytokines for cytotoxic function to eliminate tumor cells.

[00242] In some embodiments, payloads of the present invention may be cytokines, and fragments, variants, analogs and derivatives thereof, including but not limited to interleukins, tumor necrosis factors (TNFs), interferons (IFNs), TGF beta and chemokines. In some embodiments, payloads of the present invention may be cytokines that stimulate immune responses. In other embodiments, payloads of the invention may be antagonists of cytokines that negatively impact anti-cancer immune responses.

[00243] In some embodiments, payloads of the present invention may be cytokine receptors, recombinant receptors, variants, analogs and derivatives thereof; or signal components of cytokines.

[00244] In some embodiments, cytokines of the present invention may be utilized to improve expansion, survival, persistence, and potency of immune cells such as CD8+T_{EM}, natural killer cells and tumor infiltrating lymphocytes (TIL) cells used for immunotherapy. In other embodiments, T cells engineered with two or more DD regulated cytokines are utilized to provide kinetic control of T cell activation and tumor microenvironment remodeling. In one aspect, the present invention provides biocircuits and compositions to minimize toxicity related to cytokine therapy. Despite its success in mitigating tumor burden, systemic cytokine therapy often results in the development of severe dose limiting side effects. Two factors contribute to the observed toxicity (a) Pleiotropism, wherein cytokines affect different cells types and sometimes produce opposing effects on the same cells depending on the context (b) Cytokines have short serum half-life and thus need to be administered at high doses to achieve therapeutic

effects, which exacerbates the pleiotropic effects. In one aspect, cytokines of the present invention may be utilized to modulate cytokine expression in the event of adverse effects. In some embodiments, cytokines of the present invention may be designed to have prolonged life span or enhanced specificity to minimize toxicity.

[00245] In some embodiments, the payload of the present invention may be an interleukin (IL) cytokine. Interleukins (ILs) are a class of glycoproteins produced by leukocytes for regulating immune responses. As used herein, the term "interleukin (IL)" refers to an interleukin polypeptide from any species or source and includes the full-length protein as well as fragments or portions of the protein. In some aspects, the interleukin payload is selected from IL1, IL1alpha (also called hematopoietin-1), IL1beta (catabolin), IL1 delta, IL1epsilon, IL1eta, IL1 zeta, interleukin-1 family member 1 to 11 (IL1F1 to IL1F11), interleukin-1 homolog 1 to 4 (IL1H1 to IL1H4), IL1 related protein 1 to 3 (IL1RP1 to IL1RP3), IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL10C, IL10D, IL11, IL11a, IL11b, IL12, IL13, IL14, IL15, IL16, IL17, IL17A, Il17B, IL17C, IL17E, IL17F, IL18, IL19, IL20, IL20 like (IL20L), Il21, IL22, IL23, IL23A, IL23-p19, IL23-p40, IL24, Il25, IL26, IL27, IL28A, IL28B, IL29, IL30, IL31, IL32, IL33, IL34, IL35, IL36 alpha, IL36 beta, IL36 gamma, IL36RN, IL37, IL37a, IL37b, IL37c, IL37d, IL37e and IL38. In other aspects, the payload of the present invention may be an interleukin receptor selected from CD121a, CDw121b, IL2Rα/CD25, IL2Rβ/CD122, IL2Rγ/CD132, CDw131, CD124, CD131, CDw125, CD126, CD130, CD127, CDw210, IL8RA, IL11Rα, CD212, CD213α1, CD213α2, IL14R, IL15Rα, CDw217, IL18Rα, IL18Rβ, IL20Rα, and IL20Rβ.

[00246] In one embodiment, the payload of the invention may comprise IL12. IL12 is a heterodimeric protein of two subunits (p35, p40) that is secreted by antigen presenting cells, such as macrophages and dendritic cells. IL12 is type 1 cytokine that acts on natural killer (NK) cells, macrophages, $CD8^+$ Cytotoxic T cells, and $CD4^+$ T helper cells through STAT4 pathway to induce IFN-γ production in these effector immune cells (reviewed by Trinchieri G, *Nat Rev Immunol.* 2003; 3(2): 133–146). IL12 can promote the cytotoxic activity of NK cells and $CD8^+$ T cells, therefore has anti-tumor function. Intravenous injection of recombinant IL12 exhibited modest clinical efficacy in a handful of patients with advanced melanoma and renal cell carcinoma (Gollob et al., *Clin. Cancer Res.* 2000; 6(5):1678–1692). IL12 has been used as an adjuvant to enhance cytotoxic immunity using a melanoma antigen vaccine, or using peptide pulsed peripheral blood mononuclear cells; and to promote NK cell activity in breast cancer with trastuzumab treatment. Local delivery of IL12 to the tumor microenvironment promotes tumor regression in several tumor models. These studies all indicate that locally increased IL12 level can promote anti-tumor immunity. One major obstacle of systemic or local administration of

recombinant IL12 protein, or through oncolytic viral vectors is the severe side effects when IL12 is presented at high level. Developing a system that tightly controls IL12 level may provide a safe use of IL12 in cancer treatment.

[00247] It is understood in the art that certain gene and/or protein nomenclature for the same gene or protein may be inclusive or exclusive of punctuation such as a dash "-" or symbolic such as Greek letters. Whether these are included or excluded herein, the meaning is not meant to be changed as would be understood by one of skill in the art. For example, IL2, IL2 and IL 2 refer to the same interleukin. Likewise, TNFalpha, TNFα, TNF-alpha, TNF-α, TNF alpha and TNF α all refer to the same protein.

[00248] In one aspect, the effector module of the invention may be a DD-IL12 fusion polypeptide. This regulatable DD-IL12 fusion polypeptide may be directly used as an immunotherapeutic agent or be transduced into an immune effector cell (T cells and TIL cells) to generate modified T cells with greater *in vivo* expansion and survival capabilities for adoptive cell transfer. The need for harsh preconditioning regimens in current adoptive cell therapies may be minimized using regulated IL12 DD-IL12 may be utilized to modify tumor microenvironment and increase persistence in solid tumors that are currently refractory to tumor antigen targeted therapy. In some embodiments, CAR expressing T cells may be armored with DD regulated IL12 to relieve immunosuppression without systemic toxicity.

[00249] In some embodiments, the IL12 may be a Flexi IL12, wherein both p35 and p40 subunits, are encoded by a single cDNA that produces a single chain polypeptide. The single chain polypeptide may be generated by placing p35 subunit at the N terminus or the c terminus of the single chain polypeptide. Similarly, the p40 subunit may be at the N terminus or C terminus of the single chain polypeptide. In some embodiments, the IL12 constructs of the invention may be placed under the transcriptional control of the CMV promoter (SEQ ID NO. 716), an EF1a promoter (SEQ ID NO. 717, SEQ ID NO. 908) or a PGK promoter (SEQ ID NO. 718). Any portion of IL12 that retains one or more functions of full length or mature IL12 may be useful in the present invention. In some aspects, the DD-IL12 comprises the amino acid sequences listed in Table 11. The amino acid sequences in Table 11 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 11: DD-IL12 constructs

Description	Promoter	Amino acid Sequence	Amino acid SEQ ID NO	Nucleic Acid SEQ ID NO
p40 signal sequence	-	MCHQQLVISWFSLVFLASPLVA	719	736-744

Linker	-	GGSGG	629	679-680
Linker	-	GGGGSGGGGSGGGGS	720	910-915
Linker		GS	-	GGATCC
Spacer		ATNFSLLKQAGDVEENPGP	745	746
Furin cleavage site	-	SARNRQKRS	721	750
Furin cleavage site	-	ARNRQKRS	722	751
Modified Furin	-	ESRRVRRNKRSK	630	681-683
P2A Cleavable Peptide	-	GATNFSLLKQAGDVEENPGP	925	926
p40	-	IWELKKDVYVVELDWYPDAPGEMVVLTCD TPEEDGITWTLDQSSEVLGSGKTLTIQVKEF GDAGQYTCHKGGEVLSHSLLLLHKKEDGI WSTDILKDQKEPKNKTFLRCEAKNYSGRFT CWWLTTISTDLTFSVKSSRGSSDPQGVTCG AATLSAERVRGDNKEYEYSVECQEDSACP AAEESLPIEVMVDAVHKLKYENYTSSFFIRD IIKPDPPKNLQLKPLKNSRQVEVSWEYPDT WSTPHSYFSLTFCVQVQGKSKREKKDRVFT DKTSATVICRKNASISVRAQDRYYSSSWSE WASVPCS	723	752-761, 632-634
p40 (K217N)	-	IWELKKDVYVVELDWYPDAPGEMVVLTCD TPEEDGITWTLDQSSEVLGSGKTLTIQVKEF GDAGQYTCHKGGEVLSHSLLLLHKKEDGI WSTDILKDQKEPKNKTFLRCEAKNYSGRFT CWWLTTISTDLTFSVKSSRGSSDPQGVTCG AATLSAERVRGDNKEYEYSVECQEDSACP AAEESLPIEVMVDAVHKLKYENYTSSFFIRD IIKPDPPNNLQLKPLKNSRQVEVSWEYPDT WSTPHSYFSLTFCVQVQGKSKREKKDRVFT DKTSATVICRKNASISVRAQDRYYSSSWSE WASVPCS	747	748
p35	-	RNLPVATPDPGMFPCLHHSQNLLRAVSNM LQKARQTLEFYPCTSEEIDHEDITKDKTSTV EACLPLELTKNESCLNSRETSFITNGSCLASR KTSFMMALCLSSIYEDLKMYQVEFKTMNA KLLMDPKRQIFLDQNMLAVIDELMQALNF NSETVPQKSSLEEPDFYKTKIKLCILLHAFRI RAVTIDRVMSYLNAS	724	762-771, 1012
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	-	ISLIAALAVDYVIGMENAMPWNLPADLAW FKRNTLNKPVIMGRHTWESIGRPLPGRKNII LSSQPGTDDRVTWVKSVDEAIAACGDVPEI MVIGGGRVIEQFLPKAQKLYLTHIDAEVEG DTHFPDYEPDDWESVFSEFHDADAQNSHSY CFEILERR	9	692, 772, 814, 687, 988, 991
FKBP (F36V, L106P)	-	GVQVETISPGDGRTFPKRGQTCVVHYTGML EDGKKVDSSRDRNKPFKFMLGKQEVIRGW EEGVAQMSVGQRAKLTISPDYAYGATGHP GIIPPHATLVFDVELLKPE	11	684-686, 987, 989
FKBP (F36V, E31G, R71G, K105E)	-	GVQVETISPGDGRTFPKRGQTCVVHYTGML GDGKKVDSSRDRNKPFKFMLGKQEVIRGW EEGVAQMSVGQGAKLTISPDYAYGATGHP GIIPPHATLVFDVELLELE	12	688-691, 994, 1013, 1028
hDHFR (Amino acid 2-187 of WT; Q36F, Y122I, A125F)	-	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNE FRYFFRMTTTSSVEGKQNLVIMGKKTWFSI PEKNRPLKGRINLVLSRELKEPPQGAHFLSR SLDDALKLTEQPELANKVDMVWIVGGSSVI KEFMNHPGHLKLFVTRIMQDFESDTFFPEID	46	773

		LEKYKLLPEYPGVLSDVQEEKGIKYKFEVY EKND		
hDHFR (Amino acid 2-187 of WT) (I17V)	-	VGSLNCIVAVSQNMGVGKNGDLPWPPLRN EFRYFQRMTTTSSVEGKQNLVIMGKKTWFS IPEKNRPLKGRINLVLSRELKEPPQGAHFLS RSLDDALKLTEQPELANKVDMVWIVGGSS VYKEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYKFE VYEKND	894	979
hDHFR (Amino acid 2-187 of WT) (Y122I)	-	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNE FRYFQRMTTTSSVEGKQNLVIMGKKTWFSI PEKNRPLKGRINLVLSRELKEPPQGAHFLSR SLDDALKLTEQPELANKVDMVWIVGGSSVI KEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVY EKND	895	694, 995
OT-IL12-001 (p40 signal sequence - FKBP (F36V, L106P) - linker (GGSGG) - p40 - linker2 (G4S)3 - p35-stop)	CMV	MCHQQLVISWFSLVFLASPLVAGVQVETISP GDGRTFPKRGQTCVVHYTGMLEDGKKVDS SRDRNKPFKFMLGKQEVIRGWEEGVAQMS VGQRAKLTISPDYAYGATGHPGIIPPHATLV FDVELLKPEGGSGGIWELKKDVYVVELDW YPDAPGEMVVLTCDTPEEDGITWTLDQSSE VLGSGKTLTIQVKEFGDAGQYTCHKGGEVL SHSLLLLHKKEDGIWSTDILKDQKEPKNKTF LRCEAKNYSGRFTCWWLTTISTDLTFSVKS SRGSSDPQGVTCGAATLSAERVRGDNKEYE YSVECQEDSACPAAEESLPIEVMVDAVHKL KYENYTSSFFIRDIIKPDPPKNLQLKPLKNSR QVEVSWEYPDTWSTPHSYFSLTFCVQVQG KSKREKKDRVFTDKTSATVICRKNASISVR AQDRYYSSSWSEWASVPCSGGGGSGGGGS GGGGSRNLPVATPDPGMFPCLHHSQNLLRA VSNMLQKARQTLEFYPCTSEEIDHEDITKDK TSTVEACLPLELTKNESCLNSRETSFITNGSC LASRKTSFMMALCLSSIYEDLKMYQVEFKT MNAKLLMDPKRQIFLDQNMLAVIDELMQA LNFNSETVPQKSSLEEPDFYKTKIKLCILLH AFRIRAVTIDRVMSYLNAS*	727	774
OT-IL12-002 (Met - FKBP (F36V, L106P) - linker (GGSGG) - p40 signal sequence - p40 - linker ((G4S)3) - p35 - stop)	CMV	MGVQVETISPGDGRTFPKRGQTCVVHYTG MLEDGKKVDSSRDRNKPFKFMLGKQEVIR GWEEGVAQMSVGQRAKLTISPDYAYGATG HPGIIPPHATLVFDVELLKPEGGSGGMCHQ QLVISWFSLVFLASPLVAIWELKKDVYVVE LDWYPDAPGEMVVLTCDTPEEDGITWTLD QSSEVLGSGKTLTIQVKEFGDAGQYTCHKG GEVLSHSLLLLHKKEDGIWSTDILKDQKEP KNKTFLRCEAKNYSGRFTCWWLTTISTDLT FSVKSSRGSSDPQGVTCGAATLSAERVRGD NKEYEYSVECQEDSACPAAEESLPIEVMVD AVHKLKYENYTSSFFIRDIIKPDPPKNLQLK PLKNSRQVEVSWEYPDTWSTPHSYFSLTFC VQVQGKSKREKKDRVFTDKTSATVICRKN ASISVRAQDRYYSSSWSEWASVPCSGGGGS GGGGSGGGGSRNLPVATPDPGMFPCLHHS QNLLRAVSNMLQKARQTLEFYPCTSEEIDH EDITKDKTSTVEACLPLELTKNESCLNSRET SFITNGSCLASRKTSFMMALCLSSIYEDLKM YQVEFKTMNAKLLMDPKRQIFLDQNMLAV IDELMQALNFNSETVPQKSSLEEPDFYKTKI KLCILLHAFRIRAVTIDRVMSYLNAS*	728	775

OT-IL12-003 (p40 signal sequence - FKBP (F36V, L106P)- furin (SARNRQKRS) - p40- linker ((G4S)3)- p35 - stop)	CMV	MCHQQLVISWFSLVFLASPLVAGVQVETISP GDGRTFPKRGQTCVVHYTGMLEDGKKVDS SRDRNKPFKFMLGKQEVIRGWEEGVAQMS VGQRAKLTISPDYAYGATGHPGIIPPHATLV FDVELLKPESARNRQKRSIWELKKDVYVVE LDWYPDAPGEMVVLTCDTPEEDGITWTLD QSSEVLGSGKTLTIQVKEFGDAGQYTCHKG GEVLSHSLLLLHKKEDGIWSTDILKDQKEP KNKTFLRCEAKNYSGRFTCWWLTTISTDLT FSVKSSRGSSDPQGVTCGAATLSAERVRGD NKEYEYSVECQEDSACPAAEESLPIEVMVD AVHKLKYENYTSSFFIRDIIKPDPPKNLQLK PLKNSRQVEVSWEYPDTWSTPHSYFSLTFC VQVQGKSKREKKDRVFTDKTSATVICRKN ASISVRAQDRYYSSSWSEWASVPCSGGGGS GGGGSGGGGSRNLPVATPDPGMFPCLHHS QNLLRAVSNMLQKARQTLEFYPCTSEEIDH EDITKDKTSTVEACLPLELTKNESCLNSRET SFITNGSCLASRKTSFMMALCLSSIYEDLKM YQVEFKTMNAKLLMDPKRQIFLDQNMLAV IDELMQALNFNSETVPQKSSLEEPDFYKTKI KLCILLHAFRIRAVTIDRVMSYLNAS*	729	776
OT-IL12-004 (p40 signal sequence - p40 - linker ((G4S)3) - p35 - furin (ARNRQKRS) - FKBP (E31G, F36V, R71G, K105E) -stop)	CMV	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS ARNRQKRSGVQVETISPGDGRTFPKRGQTC VVHYTGMLGDGKKVDSSRDRNKPFKFML GKQEVIRGWEEGVAQMSVGQGAKLTISPD YAYGATGHPGIIPPHATLVFDVELLELE*	730	777
OT-IL12-005 (p40 signal sequence- p40 -- linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	CMV	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN	731	778

		MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQRAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*		
OT-IL12-006 (p40 signal sequence- p40 – linker ((G4S)3)- p35 - stop)	CMV	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS *	732	779
OT-IL12-007 (p40 signal sequence; ecDHFR (Amino acid 2-159 of WT) (R12Y, 100I) - furin site (ESRRVRRNK RSK) - p40 – linker ((G4S)3) - p35)	CMV	MCHQQLVISWFSLVFLASPLVAISLIAALAV DYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTD DRVTWVKSVDEAIAACGDVPEIMVIGGGR VIEQFLPKAQKLYLTHIDAEVEGDTHFPDYE PDDWESVFSEFHDADAQNSHSYCFEILERR ESRRVRRNKRSKIWELKKDVYVVELDWYP DAPGEMVVLTCDTPEEDGITWTLDQSSEVL GSGKTLTIQVKEFGDAGQYTCHKGGEVLSH SLLLLHKKEDGIWSTDILKDQKEPKNKTFLR CEAKNYSGRFTCWWLTTISTDLTFSVKSSR GSSDPQGVTCGAATLSAERVRGDNKEYEY SVECQEDSACPAAEESLPIEVMVDAVHKLK YENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQ VEVSWEYPDTWSTPHSYFSLTFCVQVQGKS KREKKDRVFTDKTSATVICRKNASISVRAQ DRYYSSSWSEWASVPCSGGGGSGGGGSGG GGSRNLPVATPDPGMFPCLHHSQNLLRAVS NMLQKARQTLEFYPCTSEEIDHEDITKDKTS TVEACLPLELTKNESCLNSRETSFITNGSCL ASRKTSFMMALCLSSIYEDLKMYQVEFKT MNAKLLMDPKRQIFLDQNMLAVIDELMQA LNFNSETVPQKSSLEEPDFYKTKIKLCILLH AFRIRAVTIDRVMSYLNAS	733	780
OT-IL12-008 (p40 signal sequence; hDHFR (Amino acid 2-187 of WT) (Q36K, Y122I, A125F) - furin site (ESRRVRRNK RSK)- p40 -	CMV	MCHQQLVISWFSLVFLASPLVAVGSLNCIV AVSQNMGIGKNGDLPWPPLRNEFRYFFRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPL KGRINLVLSRELKEPPQGAHFLSRSLDDALK LTEQPELANKVDMVWIVGGSSVIKEFMNHP GHLKLFVTRIMQDFESDTFFPEIDLEKYKLL PEYPGVLSDVQEEKGIKYKFEVYEKNDESR RVRRNKRSKIWELKKDVYVVELDWYPDAP GEMVVLTCDTPEEDGITWTLDQSSEVLGSG KTLTIQVKEFGDAGQYTCHKGGEVLSHSLL LLHKKEDGIWSTDILKDQKEPKNKTFLRCE	734	781

linker((G4S)3) - p35)		AKNYSGRFTCWWLTTISTDLTFSVKSSRGS SDPQGVTCGAATLSAERVRGDNKEYEYSV ECQEDSACPAAEESLPIEVMVDAVHKLKYE NYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVE VSWEYPDTWSTPHSYFSLTFCVQVQGKSKR EKKDRVFTDKTSATVICRKNASISVRAQDR YYSSSWSEWASVPCSGGGGSGGGGSGGGG SRNLPVATPDPGMFPCLHHSQNLLRAVSNM LQKARQTLEFYPCTSEEIDHEDITKDKTSTV EACLPLELTKNESCLNSRETSFITNGSCLASR KTSFMMALCLSSIYEDLKMYQVEFKTMNA KLLMDPKRQIFLDQNMLAVIDELMQALNF NSETVPQKSSLEEPDFYKTKIKLCILLHAFRI RAVTIDRVMSYLNAS		
OT-IL12-009 (p40 signal sequence- p40 – linker ((G4S)3) - p35 - furin (ESRRVRRNK RSK) - FKBP (E31G, F36V, R71G, K105E)- stop)	CMV	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS ESRRVRRNKRSKGVQVETISPGDGRTFPKR GQTCVVHYTGMLGDGKKVDSSRDRNKPFK FMLGKQEVIRGWEEGVAQMSVGQGAKLTI SPDYAYGATGHPGIIPPHATLVFDVELLELE *	735	782
OT-IL12-019 (p40 signal sequence- p40- linker((G4S)3)- p35-stop)	PGK	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS *	732	779
OT-IL12-020 (p40 signal sequence- p40-	EF1a	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD	732	779

linker((G4S)3)-p35-stop)		QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS *		
OT-IL12-021 (p40 signal sequence- p40-linker((G4S)3)-p35-stop)	No promoter	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS *	732	779
OT-IL12-022 (p40 signal sequence- p40 – linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	PGK	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*	731	778
OT-IL12-023 (p40 signal sequence- p40 – linker-	EF1a	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD	731	778

((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)		QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*		
OT-IL12-024 (p40 signal sequence- p40 – linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	No promoter	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*	731	778
OT-IL12-025 (p40 signal sequence- p40 – linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	PGK	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV	731	778

		IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*		
OT-IL12-026 (p40 signal sequence- p40 – linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	EF1a	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*	731	778
OT-IL12-027 (p40 signal sequence- p40 – linker- ((G4S)3) - p35 - linker (GGSG) - FKBP (E31G, F36V, R71G, K105E) - stop)	No promoter	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS GGSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGA TGHPGIIPPHATLVFDVELLELE*	731	778
OT-IL12-028 (p40 signal sequence - p40 - linker ((G4S)3) - p35 - furin (ARNRQKRS) - FKBP (E31G, F36V, R71G, K105E) -stop)	PGK	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS	730	777

		RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS ARNRQKRSGVQVETISPGDGRTFPKRGQTC VVHYTGMLGDGKKVDSSRDRNKPFKFML GKQEVIRGWEEGVAQMSVGQGAKLTISPD YAYGATGHPGIIPPHATLVFDVELLELE*		
OT-IL12-029 (p40 signal sequence- p40 – linker ((G4S)3) - p35 - furin (ESRRVRRNK RSK) - FKBP (E31G, F36V, R71G, K105E)-stop)	EF1a	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS ESRRVRRNKRSKGVQVETISPGDGRTFPKR GQTCVVHYTGMLGDGKKVDSSRDRNKPFK FMLGKQEVIRGWEEGVAQMSVGQGAKLTI SPDYAYGATGHPGIIPPHATLVFDVELLELE *	735	782
OT-IL12-030 (p40 signal sequence- p40 – linker ((G4S)3) - p35 - furin (ESRRVRRNK RSK) - FKBP (E31G, F36V, R71G, K105E)-stop)	No promoter	MCHQQLVISWFSLVFLASPLVAIWELKKDV YVVELDWYPDAPGEMVVLTCDTPEEDGIT WTLDQSSEVLGSGKTLTIQVKEFGDAGQYT CHKGGEVLSHSLLLLHKKEDGIWSTDILKD QKEPKNKTFLRCEAKNYSGRFTCWWLTTIS TDLTFSVKSSRGSSDPQGVTCGAATLSAER VRGDNKEYEYSVECQEDSACPAAEESLPIE VMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPDTWSTPHSYFS LTFCVQVQGKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYYSSSWSEWASVPCSGG GGSGGGGSGGGGSRNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEE IDHEDITKDKTSTVEACLPLELTKNESCLNS RETSFITNGSCLASRKTSFMMALCLSSIYED LKMYQVEFKTMNAKLLMDPKRQIFLDQN MLAVIDELMQALNFNSETVPQKSSLEEPDF YKTKIKLCILLHAFRIRAVTIDRVMSYLNAS ESRRVRRNKRSKGVQVETISPGDGRTFPKR GQTCVVHYTGMLGDGKKVDSSRDRNKPFK FMLGKQEVIRGWEEGVAQMSVGQGAKLTI SPDYAYGATGHPGIIPPHATLVFDVELLELE *	735	782
OT-IL12-046 (p40 signal sequence – FKBP (F36V, L106P) – Linker	EF1a	MCHQQLVISWFSLVFLASPLVAGVQVETISP GDGRTFPKRGQTCVVHYTGMLEDGKKVDS SRDRNKPFKFMLGKQEVIRGWEEGVAQMS VGQRAKLTISPDYAYGATGHPGIIPPHATLV FDVELLKPEGGSGGIWELKKDVYVVELDW YPDAPGEMVVLTCDTPEEDGITWTLDQSSE	727	774

(GGSGG) – p40 – Linker ((G4S)3) – p35 - stop)		VLGSGKTLTIQVKEFGDAGQYTCHKGGEVL SHSLLLLHKKEDGIWSTDILKDQKEPKNKTF LRCEAKNYSGRFTCWWLTTISTDLTFSVKSS RGSSDPQGVTCGAATLSAERVRGDNKEYE YSVECQEDSACPAAEESLPIEVMVDAVHKL KYENYTSSFFIRDIIKPDPPKNLQLKPLKNSR QVEVSWEYPDTWSTPHSYFSLTFCVQVQGK SKREKKDRVFTDKTSATVICRKNASISVRAQ DRYYSSSWSEWASVPCSGGGGSGGGGSGG GGSRNLPVATPDPGMFPCLHHSQNLLRAVS NMLQKARQTLEFYPCTSEEIDHEDITKDKTS TVEACLPLELTKNESCLNSRETSFITNGSCLA SRKTSFMMALCLSSIYEDLKMYQVEFKTMN AKLLMDPKRQIFLDQNMLAVIDELMQALNF NSETVPQKSSLEEPDFYKTKIKLCILLHAFRI RAVTIDRVMSYLNAS*		

[00250] In one embodiment, the payload of the invention may comprise IL15. Interleukin 15 is a potent immune stimulatory cytokine and an essential survival factor for T cells, and Natural Killer cells. Preclinical studies comparing IL2 and IL15, have shown than IL15 is associated with less toxicity than IL2. In some embodiments, the effector module of the invention may be a DD-IL15 fusion polypeptide. IL15 polypeptide may also be modified to increase its binding affinity for the IL15 receptor. For example, the asparagine may be replaced by aspartic acid at position 72 of IL15 (SEQ ID NO. 2 of US patent publication US20140134128A1; the contents of which are incorporated by reference in their entirety). In some embodiments, the IL15 constructs of the invention may be placed under the transcriptional control of the CMV promoter (SEQ ID NO. 716), an EF1a promoter (SEQ ID NO. 717, SEQ ID NO. 908) or a PGK promoter (SEQ ID NO. 718). In some aspects, the DD-IL15 comprises the amino acid sequences listed in Table 12. The amino acid sequences in Table 12 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 12: DD IL15 constructs

Description/ Construct ID	Promoter	Amino Acid Sequence	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO
IL2 signal sequence	-	MYRMQLLSCIALSLALVTNS	783	788-791
IgE Leader	-	MDWTWILFLVAAATRVHS	801	810, 930, 931
Linker	-	EFSTEF	784	792-793
Linker	-	GGSGG	629	676-680
HA Tag	-	YPYDVPDYA	1024	1025-1027
BamHI	-	GS	-	GGATCC
P2A Cleavable Peptide	-	GATNFSLLKQAGDVEENPGP	925	926
mCherry (M1L)	-	LSKGEEDNMAIIKEFMRFKVHMEGSVNG HEFEIEGEGEGRPYEGTQTAKLKVTKGGP LPFAWDILSPQFMYGSKAYVKHPADIPDY LKLSFPEGFKWERVMNFEDGGVVTVTQD SSLQDGEFIYKVKLRGTNFPSDGPVMQKK	1029	1030

		TMGWEASSERMYPEDGALKGEIKQRLKL KDGGHYDAEVKTTYKAKKPVQLPGAYN VNIKLDITSHNEDYTIVEQYERAEGRHSTG GMDELYK		
IL15	-	NWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECEE LEEKNIKEFLQSFVHIVQMFINTS*	785	794-797, 1001
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	-	ISLIAALAVDYVIGMENAMPWNLPADLA WFKRNTLNKPVIMGRHTWESIGRPLPGRK NIILSSQPGTDDRVTWVKSVDEAIAACGD VPEIMVIGGGRVIEQFLPKAQKLYLTHIDA EVEGDTHFPDYEPDDWESVFSEFHDADA QNSHSYCFEILERR*	9	692, 772, 814, 687, 988, 991
hDHFR (Amino acid 2-187 of WT) (Y122I)	-	VGSLNCIVAVSQNMGIGKNGDLPWPPLR NEFRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGA HFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFE SDTFFPEIDLEKYKLLPEYPGVLSDVQEEK GIKYKFEVYEKND	895	694, 995
OT-IL15-001 (IL2 signal sequence-IL15-stop)	CMV	MYRMQLLSCIALSLALVTNSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL QSFVHIVQMFINTS*	786	799
OT-IL15-002 (IL2 signal sequence-linker[EFSTEF]-ecDHFR (amino acid 2-159 of WT, R12Y, 100I)- linker [GGSGG]- IL15-stop)	CMV	MYRMQLLSCIALSLALVTNSEFSTEFISLIA ALAVDYVIGMENAMPWNLPADLAWFKR NTLNKPVIMGRHTWESIGRPLPGRKNIILS SQPGTDDRVTWVKSVDEAIAACGDVPEI MVIGGGRVIEQFLPKAQKLYLTHIDAEVE GDTHFPDYEPDDWESVFSEFHDADAQNS HSYCFEILERRGGSGGNWVNVISDLKKIE DLIQSMHIDATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVENLIILANNS LSSNGNVTESGCKECEELEEKNIKEFLQSF VHIVQMFINTS*	787	800
OT-IL15-062 (IgE leader – HA Tag – IL15 – BamHI (GS) – stop)	EF1a	MDWTWILFLVAAATRVHSYPYDVPDYA NWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECEE LEEKNIKEFLQSFVHIVQMFINTSGS*	631	749
OT-IL15-132 (IgE leader –IL15 – BamHI (GS) – P2A cleavable peptide – mCherry (M1L) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDLK KIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL QSFVHIVQMFINTSGSGATNFSLLKQAGD VEENPGPLSKGEEDNMAIIKEFMRFKVHM EGSVNGHEFEIEGEGEGRPYEGTQTAKLK VTKGGPLPFAWDILSPQFMYGSKAYVKH PADIPDYLKLSFPEGFKWERVMNFEDGGV VTVTQDSSLQDGEFIYKVKLRGTNFPSDG PVMQKKTMGWEASSERMYPEDGALKGEI KQRLKLKDGGHYDAEVKTTYKAKKPVQ LPGAYNVNIKLDITSHNEDYTIVEQYERAE GRHSTGGMDELYK*	725	1055
OT-IL15-134 (IgE leader –IL15 – Linker (GS) – hDHFR (WT 2-187, Y122I) –	EF1a	MDWTWILFLVAAATRVHSNWVNVISDLK KIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL	726	1056

BamHI (GS) – P2A cleavable peptide – mCherry (M1L) - stop)		QSFVHIVQMFINTSGSVGSLNCIVAVSQN MGIGKNGDLPWPPLRNEFRYFQRMTTTSS VEGKQNLVIMGKKTWFSIPEKNRPLKGRI NLVLSRELKEPPQGAHFLSRSLDDALKLT EQPELANKVDMVWIVGGSSVIKEAMNHP GHLKLFVTRIMQDFESDTFFPEIDLEKYKL LPEYPGVLSDVQEEKGIKYKFEVYEKNDG SGATNFSLLKQAGDVEENPGPLSKGEEDN MAIIKEFMRFKVHMEGSVNGHEFEIEGEG EGRPYEGTQTAKLKVTKGGPLPFAWDILS PQFMYGSKAYVKHPADIPDYLKLSFPEGF KWERVMNFEDGGVVTVTQDSSLQDGEFI YKVKLRGTNFPSDGPVMQKKTMGWEAS SERMYPEDGALKGEIKQRLKLKDGGHYD AEVKTTYKAKKPVQLPGAYNVNIKLDITS HNEDYTIVEQYERAEGRHSTGGMDELYK *		
Description/ Construct ID	**Promoter**	**Amino Acid Sequence**	**Amino Acid SEQ ID NO**	**Nucleic Acid SEQ ID NO**
IL2 signal sequence	-	MYRMQLLSCIALSLALVTNS	783	788-791
IgE Leader	-	MDWTWILFLVAAATRVHS	801	810, 930, 931
Linker	-	EFSTEF	784	792-793
Linker	-	GGSGG	629	676-680
HA Tag	-	YPYDVPDYA	1024	1025-1027
BamHI	-	GS	-	GGATCC
P2A Cleavable Peptide	-	GATNFSLLKQAGDVEENPGP	925	926
mCherry (M1L)	-	LSKGEEDNMAIIKEFMRFKVHMEGSVNG HEFEIEGEGEGRPYEGTQTAKLKVTKGGP LPFAWDILSPQFMYGSKAYVKHPADIPDY LKLSFPEGFKWERVMNFEDGGVVTVTQD SSLQDGEFIYKVKLRGTNFPSDGPVMQKK TMGWEASSERMYPEDGALKGEIKQRLKL KDGGHYDAEVKTTYKAKKPVQLPGAYN VNIKLDITSHNEDYTIVEQYERAEGRHSTG GMDELYK	1029	1030
IL15	-	NWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECEE LEEKNIKEFLQSFVHIVQMFINTS*	785	794-797, 1001
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	-	ISLIAALAVDYVIGMENAMPWNLPADLA WFKRNTLNKPVIMGRHTWESIGRPLPGRK NIILSSQPGTDDRVTWVKSVDEAIAACGD VPEIMVIGGGRVIEQFLPKAQKLYLTHIDA EVEGDTHFPDYEPDDWESVFSEFHDADA QNSHSYCFEILERR*	9	692, 772, 814, 687, 988, 991
hDHFR (Amino acid 2-187 of WT) (Y122I)	-	VGSLNCIVAVSQNMGIGKNGDLPWPPLR NEFRYFQRMTTTSSVEGKQNLVIMGKKT WFSIPEKNRPLKGRINLVLSRELKEPPQGA HFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFE SDTFFPEIDLEKYKLLPEYPGVLSDVQEEK GIKYKFEVYEKND	895	694, 995
OT-IL15-001 (IL2 signal sequence-IL15-stop)	CMV	MYRMQLLSCIALSLALVTNSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL QSFVHIVQMFINTS*	786	799

OT-IL15-002 (IL2 signal sequence-linker[EFSTEF]-ecDHFR (amino acid 2-159 of WT, R12Y, 100I)- linker [GGSGG]- IL15-stop)	CMV	MYRMQLLSCIALSLALVTNSEFSTEFISLIA ALAVDYVIGMENAMPWNLPADLAWFKR NTLNKPVIMGRHTWESIGRPLPGRKNIILS SQPGTDDRVTWVKSVDEAIAACGDVPEI MVIGGGRVIEQFLPKAQKLYLTHIDAEVE GDTHFPDYEPDDWESVFSEFHDADAQNS HSYCFEILERRGGSGGNWVNVISDLKKIE DLIQSMHIDATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVENLIILANNS LSSNGNVTESGCKECEELEEKNIKEFLQSF VHIVQMFINTS*	787	800
OT-IL15-062 (IgE leader – HA Tag – IL15 – BamHI (GS) – stop)	EF1a	MDWTWILFLVAAATRVHSYPYDVPDYA NWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIH DTVENLIILANNSLSSNGNVTESGCKECEE LEEKNIKEFLQSFVHIVQMFINTSGS*	631	749
OT-IL15-132 (IgE leader –IL15 – BamHI (GS) – P2A cleavable peptide – mCherry (M1L) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDLK KIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL QSFVHIVQMFINTSGSGATNFSLLKQAGD VEENPGPLSKGEEDNMAIIKEFMRFKVHM EGSVNGHEFEIEGEGEGRPYEGTQTAKLK VTKGGPLPFAWDILSPQFMYGSKAYVKH PADIPDYLKLSFPEGFKWERVMNFEDGGV VTVTQDSSLQDGEFIYKVKLRGTNFPSDG PVMQKKTMGWEASSERMYPEDGALKGEI KQRLKLKDGGHYDAEVKTTYKAKKPVQ LPGAYNVNIKLDITSHNEDYTIVEQYERAE GRHSTGGMDELYK*	725	1055
OT-IL15-134 (IgE leader –IL15 – Linker (GS) – hDHFR (WT 2-187, Y122I) – BamHI (GS) – P2A cleavable peptide – mCherry (M1L) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDLK KIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILA NNSLSSNGNVTESGCKECEELEEKNIKEFL QSFVHIVQMFINTSGSVGSLNCIVAVSQN MGIGKNGDLPWPPLRNEFRYFQRMTTTSS VEGKQNLVIMGKKTWFSIPEKNRPLKGRI NLVLSRELKEPPQGAHFLSRSLDDALKLT EQPELANKVDMVWIVGGSSVIKEAMNHP GHLKLFVTRIMQDFESDTFFPEIDLEKYKL LPEYPGVLSDVQEEKGIKYKFEVYEKNDG SGATNFSLLKQAGDVEENPGPLSKGEEDN MAIIKEFMRFKVHMEGSVNGHEFEIEGEG EGRPYEGTQTAKLKVTKGGPLPFAWDILS PQFMYGSKAYVKHPADIPDYLKLSFPEGF KWERVMNFEDGGVVTVTQDSSLQDGEFI YKVKLRGTNFPSDGPVMQKKTMGWEAS SERMYPEDGALKGEIKQRLKLKDGGHYD AEVKTTYKAKKPVQLPGAYNVNIKLDITS HNEDYTIVEQYERAEGRHSTGGMDELYK *	726	1056

[00251] A unique feature of IL15 mediated activation is the mechanism of trans-presentation in which IL15 is presented as a complex with the alpha subunit of IL15 receptor (IL15Ra) that binds to and activates membrane bound IL15 beta/gamma receptor, either on the same cell or a different cell. The IL15/IL15Ra complex is more effective in activating IL15 signaling, than

IL15 by itself. Thus, in some embodiments, the effector module of the invention may include a DD-IL15/IL15Ra fusion polypeptide. In one embodiment, the payload may be IL15/IL15Ra fusion polypeptide described in US Patent Publication NO.: US20160158285A1 (the contents of which are incorporated herein by reference in their entirety). The IL15 receptor alpha comprises an extracellular domain called the sushi domain which contains most of the structural elements necessary for binding to IL15. Thus, in some embodiments, payload may be the IL15/IL15Ra sushi domain fusion polypeptide described in US Patent Publication NO.: US20090238791A1 (the contents of which are incorporated herein by reference in their entirety).

[00252] Regulated IL15/IL15Ra may be used to promote expansion, survival and potency of $CD8T_{EM}$ cell populations without impacting regulatory T cells, NK cells and TIL cells. In one embodiment, DD-IL15/IL15Ra may be utilized to enhance CD19 directed T cell therapies in B cell leukemia and lymphomas. In one aspect, IL15/IL15Ra may be used as payload of the invention to reduce the need for pre-conditioning regimens in current CAR-T treatment paradigms.

[00253] The effector modules containing DD-IL15, DD-IL15/IL15Ra and/or DD-IL15/IL15Ra sushi domain may be designed to be secreted (using e.g. IL2 signal sequence) or membrane bound (using e.g. IgE or CD8a signal sequence).

[00254] In some aspects, the DD-IL115/IL15Ra comprises the amino acid sequences provided in Table 13a, 13b, and 13c. The amino acid sequences in Tables 13a, 13b and 13c may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 13a: DD-IL15/IL15Ra construct sequences

Description/ Construct ID	Amino Acid Sequence	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO
IgE leader	MDWTWILFLVAAATRVHS	801	810, 930, 931
IL15RA Leader	MAPRRARGCRTLGLPALLLLLLLRPPATRG	932	933
Linker (SG3-(SG4)3-SG3-SLQ)	SGGGSGGGGSGGGGSGGGGSGGGSLQ	802	811, 916-920, 1002
Linker (SG3S)	SGGGS	827	828, 844, 909
Linker (SG3(SG4)5SG3S)	SGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGS	921	923
Linker	SGGGSGGGGSGGGGSGGGGS	922	924
Linker	GS	-	GGTTCC
Linker	SG	-	AGCGGC
Linker	GSG	-	GGATCCGGA or GGATCCGGT
Spacer	-	-	927-929, 1000, TCGCGAATG, TCGCA

IL15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSN GNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS*	785	794-797, 1001
IL15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPA PPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATT AAIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKN WELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLS AVSLLACYLKSRQTPPLASVEMEAMEALPVTWGTSS RDEDLENCSHHL*	803	812-813, 1003
IL15Ra (31-205 of Uniprot ID: Q13261.1)	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPA PPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTA AIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKN WELTASASHQPPGVYPQGHSDTT	1057	1058
mCherry	MSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEG EGRPYEGTQTAKLKVTKGGPLPFAWDILSPQFMYGSK AYVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVT VTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMG WEASSERMYPEDGALKGEIKQRLKLKDGGHYDAEVK TTYKAKKPVQLPGAYNVNIKLDITSHNEDYTIVEQYE RAEGRHSTGGMDELYK*	1059	1060
mCherry (M1L)	LSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEG EGRPYEGTQTAKLKVTKGGPLPFAWDILSPQFMYGSK AYVKHPADIPDYLKLSFPEGFKWERVMNFEDGGVVT VTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMG WEASSERMYPEDGALKGEIKQRLKLKDGGHYDAEVK TTYKAKKPVQLPGAYNVNIKLDITSHNEDYTIVEQYE RAEGRHSTGGMDELYK	1029	1030
HA Tag	YPYDVPDYA	1024	1025-1027
Flag	DYKDDDDK	1232	-
BamHI	GS	-	GGATCC
P2A Cleavable Peptide	GATNFSLLKQAGDVEENPGP	925	926
ecDHFR (Amino acid 2-159 of WT R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLN KPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWV KSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLT HIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHS YCFEILERR*	9	692, 772, 814, 687, 988, 991
ecDHFR (Amino acid 2-159 of WT R12H, E129K)	ISLIAALAVDHVIGMENAMPWNLPADLAWFKRNTLN KPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWV KSVDEAIAACGDVPEIMVIGGGRVYEQFLPKAQKLYL THIDAEVEGDTHFPDYKPDDWESVFSEFHDADAQNS HSYCFEILERR*	10	798, 815, 993
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQG AKLTISPDYAYGATGHPGIIPPHATLVFDVELLELE*	12	688-691, 994, 1013, 1028
hDHFR (Amino acid 2-187 of WT; Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVIKEFMNHPGHLKLFVTRIMQDFESDTF FPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKN D*	890	696, 973, 974, 996
hDHFR (Amino acid 2-187 of WT; Q36F, N65F, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFFRM TTTSSVEGKQNLVIMGKKTWFSIPEKFRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMV WIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPE IDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	891	700, 975, 976, 998

hDHFR (Amino acid 2-187 of WT; K185E)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDT FFPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEE ND*	889	972
hDHFR (Amino acid 2-187 of WT; E162G, I176F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDT FFPEIDLEKYKLLPGYPGVLSDVQEEKGFKYKFEVYE KND*	888	970-972
hDHFR (Amino acid 2-187 of WT; N127Y)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVYKEAMYHPGHLKLFVTRIMQDFESDT FFPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEK ND	892	977
hDHFR (Amino acid 2-187 of WT; I17V)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDT FFPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEK ND	894	979
hDHFR (Amino acid 2-187 of WT; I17V, Y122I)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTF FPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKN D	882	969
hDHFR (Amino acid 2-187 of WT; H131R, E144G)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVD MVWIVGGSSVYKEAMNHPGRLKLFVTRIMQDFGSDT FFPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEK ND	893	978

Table 13b: DD-IL15/IL15Ra constructs

Description	Promoter	Amino acid sequences	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO
OT-IL15-006 (IgE signal sequence; IL15; linker1 (SG3-(SG4)5-SG3); IL15Ra; linker2 (GGSGG); ecDHFR (R12H, E129K))	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGISLI AALAVDHVIGMENAMPWNLPADLAWF KRNTLNKPVIMGRHTWESIGRPLPGRKN IILSSQPGTDDRVTWVKSVDEAIAACGD	804	816

		VPEIMVIGGGRVYEQFLPKAQKLYLTHI DAEVEGDTHFPDYKPDDWESVFSEFHD ADAQNSHSYCFEILERR*		
OT-IL15-007 (IgE signal sequence; IL15; linker1 (SG3-(SG4)5-SG3); IL15Ra; linker2 (GGSGG); FKBP (E31G,F36V, R71G, K105E))	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGGVQ VETISPGDGRTFPKRGQTCVVHYTGMLG DGKKVDSSRDRNKPFKFMLGKQEVIRG WEEGVAQMSVGQGAKLTISPDYAYGAT GHPGIIPPHATLVFDVELLELE*	805	817
OT-IL15-008 (IgE signal sequence- IL15-linker (SG3-(SG4)3-SG3-SLQ)- IL15Ra-stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHL*	806	818
OT-IL15-009 (IgE signal sequence- IL15-linker (SG3-(SG4)3-SG3-SLQ)- IL15Ra-linker (SG)-ecDHFR (Amino acid 2-159 of WT; R12Y, Y100I)-stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGISLI AALAVDYVIGMENAMPWNLPADLAWF KRNTLNKPVIMGRHTWESIGRPLPGRKN IILSSQPGTDDRVTWVKSVDEAIAACGD VPEIMVIGGGRVIEQFLPKAQKLYLTHID AEVEGDTHFPDYEPDDWESVFSEFHDAD AQNSHSYCFEILERR*	807	819
OT-IL15-010 (IgE signal sequence- IL15-linker (SG3-(SG4)3-SG3-	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG	808	820

SLQ)- IL15Ra-linker (SG)-hDHFR (Y122I, A125F)-stop)		GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGVGS LNCIVAVSQNMGIGKNGDLPWPPLRNEF RYFQRMTTTSSVEGKQNLVIMGKKTWF SIPEKNRPLKGRINLVLSRELKEPPQGAH FLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEFMNHPGHLKLFVTRIMQDFE SDTFFPEIDLEKYKLLPEYPGVLSDVQEE KGIKYKFEVYEKND*		
OT-IL15-011 (IgE signal sequence- IL15-linker (SG3-(SG4)3-SG3-SLQ)- IL15Ra; linker (SG)-hDHFR (Amino acid 2-187 of WT; Q36F, N65F, Y122I)-stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGVGS LNCIVAVSQNMGIGKNGDLPWPPLRNEF RYFFRMTTTSSVEGKQNLVIMGKKTWFS IPEKFRPLKGRINLVLSRELKEPPQGAHFL SRSLDDALKLTEQPELANKVDMVWIVG GSSVIKEAMNHPGHLKLFVTRIMQDFES DTFFPEIDLEKYKLLPEYPGVLSDVQEEK GIKYKFEVYEKND*	809	821
OT-IL15-017 (IgE signal sequence- IL15-linker (SG3-(SG4)3-SG3-SLQ)- IL15Ra-linker (SG)-hDHFR (Amino acid 2-187 of WT; K185E)-stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGVGS LNCIVAVSQNMGIGKNGDLPWPPLRNEF RYFQRMTTTSSVEGKQNLVIMGKKTWF SIPEKNRPLKGRINLVLSRELKEPPQGAH FLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDF ESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEEND*	1061	1086
OT-IL15-018 (IgE signal	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT	1062	1087

sequence- IL15-linker (SG3-(SG4)3-SG3-SLQ)- IL15Ra-linker (SG)-hDHFR (Amino acid 2-187 of WT; E162G, I176F)-stop)		AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGVGS LNCIVAVSQNMGIGKNGDLPWPPLRNEF RYFQRMTTTSSVEGKQNLVIMGKKTWF SIPEKNRPLKGRINLVLSRELKEPPQGAH FLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDF ESDTFFPEIDLEKYKLLPGYPGVLSDVQE EKGFKYKFEVYEKND*	1063	1088
OT-IL15-038 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – Linker (SG) – hDHFR (Amino acid 2-187 of WT; N127Y)-stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGVGS LNCIVAVSQNMGIGKNGDLPWPPLRNEF RYFQRMTTTSSVEGKQNLVIMGKKTWF SIPEKNRPLKGRINLVLSRELKEPPQGAH FLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMYHPGHLKLFVTRIMQDF ESDTFFPEIDLEKYKLLPEYPGVLSDVQE EKGIKYKFEVYEKND*	1064	1089
OT-IL15-051 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQYPYDVPDYAITCPP PMSVEHADIWVKSYSLYSRERYICNSGF KRKAGTSSLTECVLNKATNVAHWTTPSL KCIRDPALVHQRPAPPSTVTTAGVTPQPE SLSPSGKEPAASSPSSNNTAATTAAIVPG SQLMPSKSPSTGTTEISSHESSHGTPSQTT AKNWELTASASHQPPGVYPQGHSDTTV AISTSTVLLCGLSAVSLLACYLKSRQTPP LASVEMEAMEALPVTWGTSSRDEDLEN CSHHL*	1066	1091
OT-IL15-053 (IgE leader – IL15 – Linker (SG3(SG4)5SG3	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG	1066	1091

S) – IL15Ra – Stop)		GGSGGGGSGGGGSGGGGSGGGSITCPPP MSVEHADIWVKSYSLYSRERYICNSGFK RKAGTSSLTECVLNKATNVAHWTTPSLK CIRDPALVHQRPAPPSTVTTAGVTPQPES LSPSGKEPAASSPSSNNTAATTAAIVPGS QLMPSKSPSTGTTEISSHESSHGTPSQTTA KNWELTASASHQPPGVYPQGHSDTTVAI STSTVLLCGLSAVSLLACYLKSRQTPPLA SVEMEAMEALPVTWGTSSRDEDLENCS HHL*		
OT-IL15-054 (IgE leader – IL15 – Linker (SG3(SG4)3S) – HA Tag – Linker (SG3S) – IL15Ra – Stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSYPYDVPDYASGGGSITCPPP MSVEHADIWVKSYSLYSRERYICNSGFK RKAGTSSLTECVLNKATNVAHWTTPSLK CIRDPALVHQRPAPPSTVTTAGVTPQPES LSPSGKEPAASSPSSNNTAATTAAIVPGS QLMPSKSPSTGTTEISSHESSHGTPSQTTA KNWELTASASHQPPGVYPQGHSDTTVAI STSTVLLCGLSAVSLLACYLKSRQTPPLA SVEMEAMEALPVTWGTSSRDEDLENCS HHL*	1067	1092
OT-IL15-055 (IgE leader – IL15 – Linker (SG) - IL15Ra – Stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGITCPPPMSVEH ADIWVKSYSLYSRERYICNSGFKRKAGT SSLTECVLNKATNVAHWTTPSLKCIRDP ALVHQRPAPPSTVTTAGVTPQPESLSPSG KEPAASSPSSNNTAATTAAIVPGSQLMPS KSPSTGTTEISSHESSHGTPSQTTAKNWE LTASASHQPPGVYPQGHSDTTVAISTSTV LLCGLSAVSLLACYLKSRQTPPLASVEM EAMEALPVTWGTSSRDEDLENCSHHL*	1068	1093
OT-IL15-060 (IL15Ra signal peptide – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – stop)	EF1a	MAPRRARGCRTLGLPALLLLLLLRPPAT RGNWVNVISDLKKIEDLIQSMHIDATLYT ESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTVENLIILANNSLSSNGNVTESG CKECEELEEKNIKEFLQSFVHIVQMFINT SSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYIC NSGFKRKAGTSSLTECVLNKATNVAHW TTPSLKCIRDPALVHQRPAPPSTVTTAGV TPQPESLSPSGKEPAASSPSSNNTAATTA AIVPGSQLMPSKSPSTGTTEISSHESSHGT PSQTTAKNWELTASASHQPPGVYPQGHS DTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDE DLENCSHHL*	1069	1094
OT-IL15-063 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra –	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL	1070	1095

BamHI (GS) - stop)		TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLGS*		
OT-IL15-064 and OT-IL15-071 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHL*	806	818
OT-IL15-066 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – Linker (SG) ecDHFR (Amino acid 2-159 of WT, R12Y, Y100I) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGISLI AALAVDYVIGMENAMPWNLPADLAWF KRNTLNKPVIMGRHTWESIGRPLPGRKN IILSSQPGTDDRVTWVKSVDEAIAACGD VPEIMVIGGGRVIEQFLPKAQKLYLTHID AEVEGDTHFPDYEPDDWESVFSEFHDAD AQNSHSYCFEILERR*	807	819
OT-IL15-067 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – Linker (SG) - ecDHFR (Amino acid 2-159 of WT, R12Y, Y100I) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSGISLI AALAVDYVIGMENAMPWNLPADLAWF KRNTLNKPVIMGRHTWESIGRPLPGRKN IILSSQPGTDDRVTWVKSVDEAIAACGD VPEIMVIGGGRVIEQFLPKAQKLYLTHID	1071	1098

		AEVEGDTHFPDYEPDDWESVFSEFHDAD AQNSHSYCFEILERR*		
OT-IL15-070 (IL15Ra signal peptide – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – stop)	EF1a	MAPRRARGCRTLGLPALLLLLLLRPPAT RGNWVNVISDLKKIEDLIQSMHIDATLYT ESDVHPSCKVTAMKCFLLELQVISLESG DASIHDTVENLIILANNSLSSNGNVTESG CKECEELEEKNIKEFLQSFVHIVQMFINT SSGGGSGGGGSGGGGSGGGGSGGGSLQI TCPPPMSVEHADIWVKSYSLYSRERYIC NSGFKRKAGTSSLTECVLNKATNVAHW TTPSLKCIRDPALVHQRPAPPSTVTTAGV TPQPESLSPSGKEPAASSPSSNNTAATTA AIVPGSQLMPSKSPSTGTTEISSHESSHGT PSQTTAKNWELTASASHQPPGVYPQGHS DTTVAISTSTVLLCGLSAVSLLACYLKSR QTPPLASVEMEAMEALPVTWGTSSRDE DLENCSHHL*	1072	1101
OT-IL15-072 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHL*	806	1096
OT-IL15-089 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – linker (GSG) – ecDHFR (Amino acid 2-159 of WT, R12Y, Y100I) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGISLIAALAVDY VIGMENAMPWNLPADLAWFKRNTLNKP VIMGRHTWESIGRPLPGRKNIILSSQPGT DDRVTWVKSVDEAIAACGDVPEIMVIGG GRVIEQFLPKAQKLYLTHIDAEVEGDTH FPDYEPDDWESVFSEFHDADAQNSHSYC FEILERR*	1074	1102
OT-IL15-109 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra – BamHI (GS) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV	1070	1095

		HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLGS*		
OT-IL15-110 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – BamHI (GS) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGS*	1075	1103
OT-IL15-114 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR (Amino acid 2-187 of WT; K185E) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVY KEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYK FEVYEEND*	1076	1104
OT-IL15-115 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR (Amino acid 2-187 of WT; E162G, I176F) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR	1077	1105

		PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVY KEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPGYPGVLSDVQEEKGFKY KFEVYEKND*		
OT-IL15-116 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR (Amino acid 2-187 of WT; H131R, E144G) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVY KEAMNHPGRLKLFVTRIMQDFGSDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYK FEVYEKND*	1078	1106
OT-IL15-117 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR(Amino acid 2-187 of WT; I17V) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVY KEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYK FEVYEKND*	1079	1107
OT-IL15-118 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR (Amino acid 2-187 of	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH	1080	1108

WT, N127Y) - stop)		ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVY KEAMYHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYK FEVYEKND*		
OT-IL15-119 (IgE leader – FLAG – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – HA Tag – IL15Ra – Linker (GSG) – hDHFR (Amino acid 2-187 of WT, I17V, Y122I) - stop)	EF1a	MDWTWILFLVAAATRVHSDYKDDDDK NWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDA SIHDTVENLIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLQSFVHIVQMFINTSSG GGSGGGGSGGGGSGGGGSGGGSLQYPY DVPDYAITCPPPMSVEHADIWVKSYSLY SRERYICNSGFKRKAGTSSLTECVLNKAT NVAHWTTPSLKCIRDPALVHQRPAPPST VTTAGVTPQPESLSPSGKEPAASSPSSNN TAATTAAIVPGSQLMPSKSPSTGTTEISSH ESSHGTPSQTTAKNWELTASASHQPPGV YPQGHSDTTVAISTSTVLLCGLSAVSLLA CYLKSRQTPPLASVEMEAMEALPVTWG TSSRDEDLENCSHHLGSGVGSLNCIVAV SQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNR PLKGRINLVLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWIVGGSSVIK EAMNHPGHLKLFVTRIMQDFESDTFFPEI DLEKYKLLPEYPGVLSDVQEEKGIKYKF EVYEKND*	1081	1109
OT-IL15-128 (IgE leader – IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra– Spacer – Flagx3 - Spacer - BamHI (GS) – P2A cleavable peptide – mCherry (M1L) - stop)	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLSRMD YKDDDDKDYKDDDDKDYKDDDDKSRG SGATNFSLLKQAGDVEENPGPLSKGEED NMAIIKEFMRFKVHMEGSVNGHEFEIEG EGEGRPYEGTQTAKLKVTKGGPLPFAW DILSPQFMYGSKAYVKHPADIPDYLKLSF PEGFKWERVMNFEDGGVVTVTQDSSLQ DGEFIYKVKLRGTNFPSDGPVMQKKTM GWEASSERMYPEDGALKGEIKQRLKLK DGGHYDAEVKTTYKAKKPVQLPGAYN VNIKLDITSHNEDYTIVEQYERAEGRHST GGMDELYK*	1082	1110
OT-IL15-129 (IgE leader –	EF1a	MDWTWILFLVAAATRVHSNWVNVISDL KKIEDLIQSMHIDATLYTESDVHPSCKVT	1083	1111

IL15 – Linker (SG3-(SG4)3-SG3-SLQ) – IL15Ra–BamHI (GS) – P2A cleavable peptide – mCherry (M1L)-stop)		AMKCFLLELQVISLESGDASIHDTVENLII LANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTSSGGGSGGGGSGG GGSGGGGSGGGSLQITCPPPMSVEHADI WVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALV HQRPAPPSTVTTAGVTPQPESLSPSGKEP AASSPSSNNTAATTAAIVPGSQLMPSKSP STGTTEISSHESSHGTPSQTTAKNWELTA SASHQPPGVYPQGHSDTTVAISTSTVLLC GLSAVSLLACYLKSRQTPPLASVEMEAM EALPVTWGTSSRDEDLENCSHHLGSGAT NFSLLKQAGDVEENPGPLSKGEEDNMAI IKEFMRFKVHMEGSVNGHEFEIEGEGEG RPYEGTQTAKLKVTKGGPLPFAWDILSP QFMYGSKAYVKHPADIPDYLKLSFPEGF KWERVMNFEDGGVVTVTQDSSLQDGEF IYKVKLRGTNFPSDGPVMQKKTMGWEA SSERMYPEDGALKGEIKQRLKLKDGGH YDAEVKTTYKAKKPVQLPGAYNVNIKL DITSHNEDYTIVEQYERAEGRHSTGGMD ELYK*		

Table 13c: IL15/IL15Ra constructs

Construct Description	Sequence Description	Promoter	Amino acid sequences	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO/ Sequence
OT-IL15-122 (IgE leader – IL15 – linker (GS) – hDHFR (Amino acid 2-187 of WT, Y122I) – stop – spacer – IRES – spacer – mCherry – stop)	Full construct	EF1a	MDWTWILFLVAAATRVHSN WVNVISDLKKIEDLIQSMHID ATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVE NLIILANNSLSSNGNVTESGC KECEELEEKNIKEFLQSFVHIV QMFINTSGSVGSLNCIVAVSQ NMGIGKNGDLPWPPLRNEFR YFQRMTTTSSVEGKQNLVIM GKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLF VTRIMQDFESDTFFPEIDLEKY KLLPEYPGVLSDVQEEKGIKY KFEVYEKND*SR*YDSLEIPPL SLPPP*RYWPKPLGIRPVCVC LYVIFHHIAVFWQCEGPETWP CLLDEHS*GSFPSRQRNARSV ECREGSSSSGSFLKTNNVCSD PLQAAEPPTWRQVPLRPKAT CIRYTCKGGTTPVPRCELDSC GKSQMALLKRIQQGAEGCPE GTPLYGI*SGASVHMLYMCL VEVKKTSRPPEPRGRGFPLKN TMIIWPQP**ARARRITWPSSR SSCASRCTWRAP*TATSSRSR ARARAAPTRAPRPPS*R*PRV APCPSPGTSCPLSSCTAPRPT*	1114, 1126-1140	1120

			STPPTSPTT*SCPSPRASSGSA* *TSRTAAW*P*PRTPPCRTASS STR*SCAAPTSPPTAP*CRRRP WAGRPPPSGCTPRTAP*RARS SRG*S*RTAATTTLRSRPPTRP RSPCSCPAPTTSTSSWTSPPTT RTTPSWNSTNAPRAATPPAA WTSCTS		
	IgE leader – IL15 – linker (GS) – hDHFR (Amino acid 2-187 of WT, Y122I) – stop	-	MDWTWILFLVAAATRVHSN WVNVISDLKKIEDLIQSMHID ATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVE NLIILANNSLSSNGNVTESGC KECEELEEKNIKEFLQSFVHIV QMFINTSGSVGSLNCIVAVSQ NMGIGKNGDLPWPPLRNEFR YFQRMTTTSSVEGKQNLVIM GKKTWFSIPEKNRPLKGRINL VLSRELKEPPQGAHFLSRSLD DALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLF VTRIMQDFESDTFFPEIDLEKY KLLPEYPGVLSDVQEEKGIKY KFEVYEKND*	1115	1121
	mCherry - stop	-	MSKGEEDNMAIIKEFMRFKV HMEGSVNGHEFEIEGEGEGRP YEGTQTAKLKVTKGGPLPFA WDILSPQFMYGSKAYVKHPA DIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGE FIYKVKLRGTNFPSDGPVMQ KKTMGWEASSERMYPEDGA LKGEIKQRLKLKDGGHYDAE VKTTYKAKKPVQLPGAYNV NIKLDITSHNEDYTIVEQYER AEGRHSTGGMDELYK*	1116	1122
OT-IL15-123 and OT-IL15-127(IgE leader – IL15 – BamHI (GS) – stop – spacer – IRES – spacer – mCherry - stop)	Full construct	EF1a	MDWTWILFLVAAATRVHSN WVNVISDLKKIEDLIQSMHID ATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVE NLIILANNSLSSNGNVTESGC KECEELEEKNIKEFLQSFVHIV QMFINTSGS*NLDNTTH*RSR PSPSPPPNVTGRSRLE*GRCAF VYMLFSTILPSFGNVRARKPG PVFLTSIPRGLSPLAKGMQGL LNVVKEAVPLEAS*RQTTSVA TLCRQRNPPPGDRCLCGQKP RV*DTPAKAAQPQCHVVSWI VVERVKWLSSSVFNKGLKDA QKVPHCMGSDLGPRCTCFTC V*SRLKKRLGPPNHGDVVFL* KTR**YGHNHDEQGRGG*HG HHQGVHALQGAHGGLRERP RVRDRGRGRGPPLRGHPDRQ AEGDQGWPPALRLGHPVPSV HVRLQGLREAPRRHPRLLEA VLPRGLQVGARDELRGRRRG DRDPGLLPAGRRVHLQGEAA RHQLPLRRPRNAEEDHGLGG	1117, 1141-1149	1123

			LLRADVPRGRRPEGRDQAEA EAEGRRPLRR*GQDHLQGQE ARAAARRLQRQHQVGHHLP QRGLHHRGTVRTRRGPPLHR RHGRAVQV		
	IgE leader – IL15 – BamHI (GS) – stop	-	MDWTWILFLVAAATRVHSN WVNVISDLKKIEDLIQSMHID ATLYTESDVHPSCKVTAMKC FLLELQVISLESGDASIHDTVE NLIILANNSLSSNGNVTESGC KECEELEEKNIKEFLQSFVHIV QMFINTSGS*	1118	1124
	mCherry - stop	-	MSKGEEDNMAIIKEFMRFKV HMEGSVNGHEFEIEGEGEGRP YEGTQTAKLKVTKGGPLPFA WDILSPQFMYGSKAYVKHPA DIPDYLKLSFPEGFKWERVM NFEDGGVVTVTQDSSLQDGE FIYKVKLRGTNFPSDGPVMQ KKTMGWEASSERMYPEDGA LKGEIKQRLKLKDGGHYDAE VKTTYKAKKPVQLPGAYNV NIKLDITSHNEDYTIVEQYER AEGRHSTGGMDELYK*	1119	1125

[00255] In one embodiment, the payload of the present invention may comprise IL18. IL18 is a proinflammatory and immune regulatory cytokine that promotes IFN-γ production by T and NK cells. IL18 belongs to the IL1 family. Secreted IL18 binds to a heterodimer receptor complex, consisting of IL18Rα and β-chains and initiates signal transduction. IL18 acts in concert with other cytokines to modulate immune system functions, including induction of IFN-γ production, Th1 responses, and NK cell activation in response to pathogen products. IL18 showed anti-cancer effects in several tumors. Administration of recombinant IL18 protein or IL18 transgene induces melanoma or sarcoma regression through the activation of $CD4^+$ T and/or NK cell-mediated responses (reviewed by Srivastava et al., *Curr. Med. Chem.*, 2010, 17: 3353–3357). The combination of IL18 with other cytokines, such as IL12 or co-stimulatory molecules (e.g., CD80) increases IL18 anti-tumor effects. For example, IL18 and IL12A/B or CD80 genes have been integrated successfully in the genome of oncolytic viruses, with the aim to trigger synergistically T cell-mediated anti-tumor immune responses (Choi et al., *Gene Ther.*, 2011, 18: 898-909). IL2/IL18 fusion proteins also display enhanced anti-tumor properties relative to either cytokine alone and low toxicity in preclinical models (Acres et al., *Cancer Res.*, 2005, 65:9536–9546).

[00256] IL18 alone, or in combination of IL12 and IL15, activates NK cells. Preclinical studies have demonstrated that adoptively transferred IL12, IL15 and IL18 pre-activated NK cells display enhanced effector function against established tumors *in vivo* (Ni et al., *J Exp Med.* 2012, 209: 2351–2365; and Romee et al., *Blood.* 2012,120:4751–4760). Human IL12/IL15/IL18

activated NK cells also display memory-like features and secrete more IFN-γ in response to cytokines (e.g., low concentration of IL2). In one embodiment, the effector module of the present invention may be a DD-IL18 fusion polypeptide.

[00257] In one embodiment, the payload of the present invention may comprise IL21. IL21 is another pleiotropic type I cytokine that is produced mainly by T cells and natural killer T (NKT) cells. IL21 has diverse effects on a variety of cell types including but not limited to $CD4^+$ and $CD8^+$ T cells, B cells, macrophages, monocytes, and dendritic cells (DCs). The functional receptor for IL21 is composed of IL21 receptor (IL21R) and the common cytokine receptor gamma chain, which is also a subunit of the receptors for IL2, IL4, IL7, IL9 and IL15. Studies provide compelling evidence that IL21 is a promising immunotherapeutic agent for cancer immunotherapy. IL21 promotes maturation, enhances cytotoxicity, and induces production of IFN-γ and perforin by NK cells. These effector functions inhibit the growth of B16 melanoma (Kasaian et al., *Immunity.* 2002, 16(4):559–569; and Brady et al., *J Immunol.*2004, 172(4):2048–2058). IL21 together with IL15 expands antigen-specific $CD8^+$ T-cell numbers and their effector function, resulting in tumor regression (Zeng et al., *J Exp Med.*2005, 201(1):139–148). IL21 may also be used to rejuvenate multiple immune effector cells in the tumor microenvironment. IL21 may also directly induce apoptosis in certain types of lymphoma such as diffuse large B-cell lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia cells, via activation of STAT3 or STAT1 signal pathway. IL21, alone or in combination with anti-CD20 mAb (rituximab) can activate NK cell-dependent cytotoxic effects. Interestingly, discovery of the immunosuppressive actions of IL21 suggests that this cytokine is a "double-edged sword"- IL21 stimulation may lead to either the induction or suppression of immune responses. Both stimulatory and suppressive effects of IL21 must be considered when using IL21-related immunotherapeutic agents. The level of IL21 needs to be tightly controlled by regulatory elements. In one aspect, the effector module of the present invention may be a DD-IL21 fusion polypeptide.

[00258] In some embodiments, payloads of the present invention may comprise type I interferons. Type I interferons (IFNs-I) are soluble proteins important for fighting viral infection in humans. IFNs-I include IFN-alpha subtypes (IFN- α1, IFN- α1b, IFN- α1c), IFN-beta, IFN-delta subtypes (IFN-delta 1, IFN-delta 2, IFN-delta 8), IFN-gamma, IFN-kappa, and IFN-epsilon, IFN-lambda, IFN-omega, IFN-tau and IFN-zeta. IFN-α and IFN-β are the main IFN-I subtypes in immune responses. All subtypes of IFN-I signal through a unique heterodimeric receptor, interferon alpha receptor (IFNAR), composed of 2 subunits, IFNAR1 and IFNAR2. IFNR activation regulates the host response to viral infections and in adaptive immunity. Several

signaling cascades can be activated by IFNR, including the Janus activated kinase–signal transducer and activation of transcription (JAK-STAT) pathway, the mitogen activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K) pathway, the v-crk sarcoma virus CT10 oncogene homolog (avian)-like (CRKL) pathway, and NF-κB cascade. It has long been established that type I IFNs directly inhibit the proliferation of tumor cells and virus-infected cells, and increase MHC class I expression, enhancing antigen recognition. IFNs-I have also proven to be involved in immune system regulation. IFNs can either directly, through interferon receptor (IFNR), or indirectly by the induction of chemokines and cytokines, regulate the immune system. Type I IFNs enhance NK cell functions and promote survival of NK cells. Type I IFNs also affect monocytes, supporting the differentiation of monocytes into DC with high capacity for antigen presentation, and stimulate macrophage function and differentiation. Several studies also demonstrate that IFNs-I promote $CD8^+$ T cell survival and functions. In some instances, it may be desirable to tune the expression of Type I IFNs using biocircuits of the present invention to avoid immunosuppression caused by long-term treatment with IFNs.

[00259] New anticancer immunotherapies are being developed that use recombinant type I IFN proteins, type I IFN transgene, type I IFN-encoding vectors and type I IFN-expressing cells. For example, IFN-α has received approval for treatment of several neoplastic diseases, such as melanoma, RCC and multiple myeloma. Though type I IFNs are powerful tools to directly and indirectly modulate the functions of the immune system, side effects of systemic long-term treatments and lack of sufficiently high efficacy have dampened the interest of IFN-α for clinical use in oncology. It is believed that if IFN levels are tightly regulated at the malignant tissues, type I IFNs are likely more efficacious. Approaches for intermittent delivery are proposed according to the observation that intermittency at an optimized pace may help to avoid signaling desensitizing mechanisms (negative feedback mechanisms) induced by IFNs-I (i.e., because of SOCS1 induction) in the responding immune cells. In accordance with the present invention, the effector module may comprise a DD-IFN fusion polypeptide. The DD and its ligand control the expression of IFN to induce an antiviral and antitumor immune responses and in the meantime, to minimize the side effects caused by long-term exposure of IFN.

[00260] In some embodiments, payloads of the present invention may comprise members of tumor necrosis factor (TNF) superfamily. The term "TNF superfamily" as used herein refers to a group of cytokines that can induce apoptosis. Members of TNF family include TNF-alpha, TNF-beta (also known as lymphotoxin-alpha (LT-α)), lymphotoxin-beta (LT-β), CD40L(CD154), CD27L (CD70), CD30L(CD153), FASL(CD178), 4-1BBL (CD137L), OX40L, TRAIL (TNF-related apoptosis inducing ligand), APRIL (a proliferation-inducing ligand), TWEAK,

TRANCE, TALL-1, GITRL, LIGHT and TNFSF1 to TNFSF20 (TNF ligand superfamily member 1 to 20). In one embodiment, the payload of the invention may be TNF-alpha. TNF-alpha can cause cytolysis of tumor cells, and induce cell proliferation differentiation as well. In one aspect, the effector module of the present invention may comprise a DD-TNF alpha fusion polypeptide.

[00261] In some embodiments, payloads of the present invention may comprise inhibitory molecules that block inhibitory cytokines. The inhibitors may be blocking antibodies specific to an inhibitory cytokine, and antagonists against an inhibitory cytokine, or the like.

[00262] In some aspects, payloads of the present invention may comprise an inhibitor of a secondary cytokine IL35. IL35 belongs to the interleukin-12 (IL12) cytokine family, and is a heterodimer composed of the IL27 β chain Ebi3 and the IL12 α chain p35. Secretion of bioactive IL35 has been described only in forkhead box protein 3 $(Foxp3)^+$ regulatory T cells (Tregs) (resting and activated Tregs). Unlike other membranes in the family, IL35 appears to function solely in an anti-inflammatory fashion by inhibiting effector T cell proliferation and perhaps other parameters (Collison et al., *Nature*, 2007, 450(7169): 566–569).

[00263] In some embodiments, payloads of the present invention may comprise inhibitors that block the transforming growth factor beta (TGF-β) subtypes (TGF-β1, TGF-β2 and TGF-β3). TGF-β is secreted by many cell types, including macrophages and is often complexed with two proteins LTBP and LAP. Serum proteinases such as plasmin catalyze the release of active TGF-β from the complex from the activated macrophages. It has been shown that an increase in expression of TGF-β correlates with the malignancy of many cancers. The immunosuppressive activity of TGF-β in the tumor microenvironment contributes to oncogenesis.

[00264] In some embodiments, payloads of the present invention may comprise inhibitors of IDO enzyme.

[00265] In some embodiments, payloads of the present invention may comprise chemokines and chemokine receptors. Chemokines are a family of secreted small cytokines, or signaling proteins that can induce directed chemotaxis in nearby responsive cells. The chemokine may be a SCY (small cytokine) selected from the group consisting of SCYA1-28 (CCL1-28), SCYB1-16 (CXCL1-16), SCYC1-2 (XCL1-2), SCYD-1 and SCYE-1; or a C chemokine selected from XCL1 and XCL2; or a CC chemokine selected from CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27 and CCL28; or a CXC chemokine selected from CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14,

CXCL15, CXCL16 and CXCL17; or a CX3C chemokine CX3CL1. In some aspects, the chemokine receptor may be a receptor for the C chemokines including XCR1; or a receptor for the CC chemokines including CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9 and CCR10; or a receptor for the CXC chemokines including CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5; or a CX3C chemokine receptor CX3CR1.

[00266] In some embodiments, payloads of the present invention may comprise other immunomodulators that play a critical role in immunotherapy, such as GM-CSF (Granulocyte-macrophage colony stimulating factor), erythropoietin (EPO), MIP3a, monocyte chemotactic protein (MCP)-1, intracellular adhesion molecule (ICAM), macrophage colony stimulating factor (M-CSF), Interleukin-1 receptor activating kinase (iRAK-1), lactotransferrin, and granulocyte colony stimulating factor (G-CSF).

[00267] In some embodiments, the payload of the present invention may comprise Amphiregulin. Amphiregulin (AREG) is an EGF-like growth factor which binds to the EGFR receptor and enhances CD4+ regulatory T cells (Tregs) function. AREG promotes immune suppression in the tumor environment. Thus, in some embodiment, the payloads of the present invention may comprise Amhiregulin to dampen immune response during immunotherapy.

[00268] In some embodiments, payloads of the present invention may comprise fusion proteins wherein a cytokine, chemokine and/or other soluble factor may be fused to other biological molecules such as antibodies and or ligands for a receptor. Such fusion molecules may increase the half-life of the cytokines, reduce systemic toxicity, and increase local concentration of the cytokines at the tumor site. Fusion proteins containing two or more cytokines, chemokines and or other soluble factors may be utilized to obtain synergistic therapeutic benefits. In one embodiment, payload may be a GM-CSF/IL2 fusion protein.

3. Additional effector module features

[00269] The effector module of the present invention may further comprise a signal sequence which regulates the distribution of the payload of interest, a cleavage and/or processing feature which facilitate cleavage of the payload from the effector module construct, a targeting and/or penetrating signal which can regulate the cellular localization of the effector module, a tag, and/or one or more linker sequences which link different components of the effector module.

Signal sequences

[00270] In addition to the SRE (e.g., DD) and payload region, effector modules of the invention may further comprise one or more signal sequences. Signal sequences (sometimes referred to as signal peptides, targeting signals, target peptides, localization sequences, transit peptides, leader sequences or leader peptides) direct proteins (e.g., the effector module of the present invention)

to their designated cellular and/or extracellular locations. Protein signal sequences play a central role in the targeting and translocation of nearly all secreted proteins and many integral membrane proteins.

[00271] A signal sequence is a short (5-30 amino acids long) peptide present at the N-terminus of the majority of newly synthesized proteins that are destined towards a particular location. Signal sequences can be recognized by signal recognition particles (SRPs) and cleaved using type I and type II signal peptide peptidases. Signal sequences derived from human proteins can be incorporated as a regulatory module of the effector module to direct the effector module to a particular cellular and/or extracellular location. These signal sequences are experimentally verified and can be cleaved (Zhang et al., *Protein Sci.* 2004, 13:2819-2824).

[00272] In some embodiments, a signal sequence may be, although not necessarily, located at the N-terminus or C-terminus of the effector module, and may be, although not necessarily, cleaved off the desired effector module to yield a "mature" payload, i.e., an immunotherapeutic agent as discussed herein.

[00273] In some examples, a signal sequence may be a secreted signal sequence derived from a naturally secreted protein, and its variant thereof. In some instances, the secreted signal sequences may be cytokine signal sequences such as, but not limited to, IL2 signal sequence comprising amino acid of SEQ ID NO: 783, encoded by the nucleotide of SEQ ID NO: 788-791 and/or p40 signal sequence comprising the amino acid sequence of SEQ ID NO: 719, encoded by the nucleotide of SEQ ID NO: 736-744.

[00274] In some instances, signal sequences directing the payload of interest to the surface membrane of the target cell may be used. Expression of the payload on the surface of the target cell may be useful to limit the diffusion of the payload to non-target *in vivo* environments, thereby potentially improving the safety profile of the payloads. Additionally, the membrane presentation of the payload may allow for physiologically and qualitative signaling as well as stabilization and recycling of the payload for a longer half-life. Membrane sequences may be the endogenous signal sequence of the N terminal component of the payload of interest. Optionally, it may be desirable to exchange this sequence for a different signal sequence. Signal sequences may be selected based on their compatibility with the secretory pathway of the cell type of interest so that the payload is presented on the surface of the T cell. In some embodiments, the signal sequence may be IgE signal sequence comprising amino acid SEQ ID NO: 801 and nucleotide sequence of SEQ ID NO: 810, 930, or 931, CD8a signal sequence (also referred to as CD8a leader) comprising amino acid SEQ ID NO: 628 and nucleotide sequence of SEQ ID NO:

671-675, or IL15Ra signal sequence (also referred to as IL15Ra leader) comprising amino acid SEQ ID NO: 932 and nucleotide sequence of SEQ ID NO: 933.

[00275] Other examples of signal sequences include, a variant may be a modified signal sequence discussed in U.S. Pat. NOs.: 8, 148, 494; 8,258,102; 9,133,265; 9,279,007; and U.S. patent application publication NO.: 20070141666; and International patent application publication NO.: WO1993018181; the contents of each of which are incorporated herein by reference in their entirety.

[00276] In other examples, a signal sequence may be a heterogeneous signal sequence from other organisms such as virus, yeast and bacteria, which can direct an effector module to a particular cellular site, such as a nucleus (e.g., EP 1209450). Other examples may include Aspartic Protease (NSP24) signal sequences from *Trichoderma* that can increase secretion of fused protein such as enzymes (e.g., U. S. Pat. NO.: 8,093,016 to Cervin and Kim), bacterial lipoprotein signal sequences (e.g., PCT application publication NO.: WO199109952 to Lau and Roux), *E.coli* enterotoxin II signal peptides (e.g., U.S. Pat. NO.: 6,605,697 to Kwon et al.), *E.coli* secretion signal sequence (e.g., U.S. patent publication NO.: US2016090404 to Malley et al.), a lipase signal sequence from a methylotrophic yeast (e.g., U.S. Pat. NO.: 8,975,041), and signal peptides for DNases derived from *Coryneform bacteria* (e.g., U.S. Pat. NO.: 4,965,197); the contents of each of which are incorporated herein by reference in their entirety.

[00277] Signal sequences may also include nuclear localization signals (NLSs), nuclear export signals (NESs), polarized cell tubulo-vesicular structure localization signals (See, e.g., U.S. Pat. NO.: 8, 993,742; Cour et al., *Nucleic Acids Res.* 2003, 31(1): 393-396; the contents of each of which are incorporated herein by reference in their entirety),extracellular localization signals, signals to subcellular locations (e.g. lysosome, endoplasmic reticulum, golgi, mitochondria, plasma membrane and peroxisomes, etc.) (See, e.g., U.S. Pat. NO.: 7,396,811; and Negi et al., *Database,* 2015, 1-7; the contents of each of which are incorporated herein by reference in their entirety).

[00278] In some embodiments, signal sequences of the present invention, include without limitation, any of those taught in Table 6 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

Cleavage sites

[00279] In some embodiments, the effector module comprises a cleavage and/or processing feature. The effector module of the present invention may include at least one protein cleavage

signal/site. The protein cleavage signal/site may be located at the N-terminus, the C-terminus, at any space between the N- and the C- termini such as, but not limited to, half-way between the N- and C-termini, between the N-terminus and the half-way point, between the half-way point and the C-terminus, and combinations thereof.

[00280] The effector module may include one or more cleavage signal(s)/site(s) of any proteinases. The proteinases may be a serine proteinase, a cysteine proteinase, an endopeptidase, a dipeptidase, a metalloproteinase, a glutamic proteinase, a threonine proteinase and an aspartic proteinase. In some aspects, the cleavage site may be a signal sequence of furin, actinidain, calpain-1, carboxypeptidase A, carboxypeptidase P, carboxypeptidase Y, caspase-1, caspase-2, caspase-3, caspase-4, caspase-5, caspase-6, caspase-7, caspase-8, caspase-9, caspase-10, cathepsin B, cathepsin C, cathepsin G, cathepsin H, cathepsin K, cathepsin L, cathepsin S, cathepsin V, clostripain, chymase, chymotrypsin, elastase, endoproteinase, enterokinase, factor Xa, formic acid, granzyme B, Matrix metallopeptidase-2, Matrix metallopeptidase-3, pepsin, proteinase K, SUMO protease, subtilisin, TEV protease, thermolysin, thrombin, trypsin and TAGZyme.

[00281] In one embodiment, the cleavage site is a furin cleavage site comprising the amino acid sequence SARNRQKRS (SEQ ID NO: 721), encoded by nucleotide sequence of SEQ ID NO: 750; or a revised furin cleavage site comprising the amino acid sequence ARNRQKRS (SEQ ID NO: 722), encoded by nucleotide sequence of SEQ ID NO: 751; or a modified furin site comprising the amino acid sequence ESRRVRRNKRSK (SEQ ID NO: 630), encoded by nucleotide sequence of SEQ ID NO: 681-683.

[00282] In some embodiments, cleavage sites of the present invention, include without limitation, any of those taught in Table 7 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

Protein tags

[00283] In some embodiments, the effector module of the invention may comprise a protein tag. The protein tag may be used for detecting and monitoring the process of the effector module. The effector module may include one or more tags such as an epitope tag (e.g., a FLAG or hemagglutinin (HA) tag). A large number of protein tags may be used for the present effector modules. They include, but are not limited to, self-labeling polypeptide tags (e.g., haloalkane dehalogenase (halotag2 or halotag7), ACP tag, clip tag, MCP tag, snap tag), epitope tags (e.g., FLAG, HA, His, and Myc), fluorescent tags (e.g., green fluorescent protein (GFP), red

fluorescent protein (RFP), yellow fluorescent protein (YFP), and its variants), bioluminescent tags (e.g. luciferase and its variants), affinity tags (e.g., maltose-binding protein (MBP) tag, glutathione-S-transferase (GST) tag), immunogenic affinity tags (e.g., protein A/G, IRS, AU1, AU5, glu-glu, KT3, S-tag, HSV, VSV-G, Xpress and V5), and other tags (e.g., biotin (small molecule), StrepTag (StrepII), SBP, biotin carboxyl carrier protein (BCCP), eXact, CBP, CYD, HPC, CBD intein-chitin binding domain, Trx, NorpA, and NusA.

[00284] In other embodiments, a tag may also be selected from those disclosed in U.S. Pat. NOs.: 8,999,897; 8,357,511; 7,094, 568; 5,011,912; 4,851,341; and 4,703,004; U.S patent application publication NOs.: US2013115635 and US2013012687; and International application publication NO.: WO2013091661; the contents of each of which are incorporated herein by reference in their entirety.

[00285] In some aspects, a multiplicity of protein tags, either the same or different tags, may be used; each of the tags may be located at the same N- or C-terminus, whereas in other cases these tags may be located at each terminus.

[00286] In some embodiments, protein tags of the present invention, include without limitation, any of those taught in Table 8 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

Targeting peptides

[00287] In some embodiments, the effector module of the invention may further comprise a targeting and/or penetrating peptide. Small targeting and/or penetrating peptides that selectively recognize cell surface markers (e.g. receptors, trans-membrane proteins, and extra-cellular matrix molecules) can be employed to target the effector module to the desired organs, tissues or cells. Short peptides (5-50 amino acid residues) synthesized *in vitro* and naturally occurring peptides, or analogs, variants, derivatives thereof, may be incorporated into the effector module for homing the effector module to the desired organs, tissues and cells, and/or subcellular locations inside the cells.

[00288] In some embodiments, a targeting sequence and/or penetrating peptide may be included in the effector module to drive the effector module to a target organ, or a tissue, or a cell (e.g., a cancer cell). In other embodiments, a targeting and/or penetrating peptide may direct the effector module to a specific subcellular location inside a cell.

[00289] A targeting peptide has any number of amino acids from about 6 to about 30 inclusive. The peptide may have 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26,

27, 28, 29 or 30 amino acids. Generally, a targeting peptide may have 25 or fewer amino acids, for example, 20 or fewer, for example 15 or fewer.

[00290] Exemplary targeting peptides may include, but are not limited to, those disclosed in the art, e.g., U.S. Pat. NOs.: 9,206,231; 9,110,059; 8,706,219; and 8,772,449; and U.S. application publication NOs.: 2016089447; 2016060296; 2016060314; 2016060312; 2016060311; 2016009772; 2016002613; 2015314011 and 2015166621; and International application publication NOs.: WO2015179691 and WO2015183044; the contents of each of which are incorporated herein by reference in their entirety.

[00291] In some embodiments, targeting peptides of the present invention, include without limitation, any of those taught in Table 9 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

Linkers

[00292] In some embodiments, the effector module of the invention may further comprise a linker sequence. The linker region serves primarily as a spacer between two or more polypeptides within the effector module. The "linker" or "spacer", as used herein, refers to a molecule or group of molecules that connects two molecules, or two parts of a molecule such as two domains of a recombinant protein.

[00293] In some embodiments, "Linker" (L) or "linker domain" or "linker region" or "linker module" or "peptide linker" as used herein refers to an oligo- or polypeptide region of from about 1 to 100 amino acids in length, which links together any of the domains/regions of the effector module (also called peptide linker). The peptide linker may be 1-40 amino acids in length, or 2-30 amino acids in length, or 20-80 amino acids in length, or 50-100 amino acids in length. Linker length may also be optimized depending on the type of payload utilized and based on the crystal structure of the payload. In some instances, a shorter linker length may be preferably selected. In some aspects, the peptide linker is made up of amino acids linked together by peptide bonds, preferably from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids: Glycine (G), Alanine (A), Valine (V), Leucine (L), Isoleucine (I), Serine (S), Cysteine (C), Threonine (T), Methionine (M), Proline (P), Phenylalanine (F), Tyrosine (Y), Tryptophan (W), Histidine (H), Lysine (K), Arginine (R), Aspartate (D), Glutamic acid (E), Asparagine (N), and Glutamine (Q). One or more of these amino acids may be glycosylated, as is understood by those in the art. In some

aspects, amino acids of a peptide linker may be selected from Alanine (A), Glycine (G), Proline (P), Asparagine (R), Serine (S), Glutamine (Q) and Lysine (K).

[00294] In one example, an artificially designed peptide linker may preferably be composed of a polymer of flexible residues like Glycine (G) and Serine (S) so that the adjacent protein domains are free to move relative to one another. Longer linkers may be used when it is desirable to ensure that two adjacent domains do not interfere with one another. The choice of a particular linker sequence may concern if it affects biological activity, stability, folding, targeting and/or pharmacokinetic features of the fusion construct. Examples of peptide linkers include, but are not limited to: MH, SG, GGSG (SEQ ID NO: 822; encoded by the nucleotide sequence SEQ ID NO: 823), GGSGG (SEQ ID NO: 629; encoded by any of the nucleotide sequences SEQ ID NO: 676-680), GGSGGG (SEQ ID NO: 824; encoded by any of the nucleotide sequences SEQ ID NO: 825-826), SGGGS (SEQ ID NO: 827; encoded by the nucleotide sequence SEQ ID NO: 828, 844, 909), GGSGGGSGG (SEQ ID NO: 829; encoded by the nucleotide sequence SEQ ID NO: 830), GGGGG (SEQ ID NO: 831), GGGGS (SEQ ID NO: 832) or (GGGGS)n (n=1 (SEQ ID NO: 832), 2 (SEQ ID NO: 833), 3 (SEQ ID NO: 720, encoded by the nucleotide sequence SEQ ID NO: 910-915), 4 (SEQ ID NO: 834), 5 (SEQ ID NO: 835), or 6 (SEQ ID NO: 836)), SSSSG (SEQ ID NO: 837) or (SSSSG)n (n=1 (SEQ ID NO: 837), 2 (SEQ ID NO: 838), 3 (SEQ ID NO: 839), 4 (SEQ ID NO: 840), 5 (SEQ ID NO: 841), or 6 (SEQ ID NO: 842)), SGGGSGGGGSGGGGSGGGGSGGGSLQ (SEQ ID NO: 802; encoded by the nucleotide sequence SEQ ID NO: 811, 916-920, 1002), EFSTEF (SEQ ID NO: 784; encoded by any of the nucleotide sequences SEQ ID NO: 792-793), GKSSGSGSESKS (SEQ ID NO: 845), GGSTSGSGKSSEGKG (SEQ ID NO: 846), GSTSGSGKSSSEGSGSTKG (SEQ ID NO: 847), GSTSGSGKPGSGEGSTKG (SEQ ID NO: 848), VDYPYDVPDYALD (SEQ ID NO: 849; encoded by nucleotide sequence SEQ ID NO: 850), EGKSSGSGSESKEF (SEQ ID NO: 851), SGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGS (SEQ ID NO: 921; encoded by SEQ ID NO: 923 SGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 922; encoded by SEQ ID NO: 924), GS (encoded by GGTTCC), SG (encoded by AGCGGC), GSG (encoded by GGATCCGGA or GGATCCGGT), or MLLLVTSLLLCELPHPAFLLIP (SEQ ID NO: 1031; encoded by SEQ ID NO: 1032).

[00295] In other examples, a peptide linker may be made up of a majority of amino acids that are sterically unhindered, such as Glycine (G) and Alanine (A). Exemplary linkers are polyglycines (such as (G)4 (SEQ ID NO: 1233), (G)5 (SEQ ID NO: 831), (G)8) (SEQ ID NO: 1234), poly(GA), and polyalanines. The linkers described herein are exemplary, and linkers that are much longer and which include other residues are contemplated by the present invention.

[00296] A linker sequence may be a natural linker derived from a multi-domain protein. A natural linker is a short peptide sequence that separates two different domains or motifs within a protein.

[00297] In some aspects, linkers may be flexible or rigid. In other aspects, linkers may be cleavable or non- cleavable. As used herein, the terms "cleavable linker domain or region" or "cleavable peptide linker" are used interchangeably. In some embodiments, the linker sequence may be cleaved enzymatically and/or chemically. Examples of enzymes (e.g., proteinase/peptidase) useful for cleaving the peptide linker include, but are not limited, to Arg-C proteinase, Asp-N endopeptidase, chymotrypsin, clostripain, enterokinase, Factor Xa, glutamyl endopeptidase, Granzyme B, Achromobacter proteinase I, pepsin, proline endopeptidase, proteinase K, Staphylococcal peptidase I, thermolysin, thrombin, trypsin, and members of the Caspase family of proteolytic enzymes (e.g. Caspases 1-10). Chemical sensitive cleavage sites may also be included in a linker sequence. Examples of chemical cleavage reagents include, but are not limited to, cyanogen bromide, which cleaves methionine residues; N-chloro succinimide, iodobenzoic acid or BNPS-skatole (2-(2-nitrophenylsulfenyl)-3-methylindole), which cleaves tryptophan residues; dilute acids, which cleave at aspartyl-prolyl bonds; and e aspartic acid-proline acid cleavable recognition sites (i.e., a cleavable peptide linker comprising one or more D-P dipeptide moieties). The fusion module may include multiple regions encoding peptides of interest separated by one or more cleavable peptide linkers.

[00298] In other embodiments, a cleavable linker may be a "self-cleaving" linker peptide, such as 2A linkers (for example T2A), 2A-like linkers or functional equivalents thereof and combinations thereof. In some embodiments, the linkers include the picornaviral 2A-like linker, CHYSEL sequences of porcine teschovirus (P2A), Thosea asigna virus (T2A) or combinations, variants and functional equivalents thereof. Other linkers will be apparent to those skilled in the art and may be used in connection with alternate embodiments of the invention. In some embodiments, the biocircuits of the present invention may include 2A peptides. The 2A peptide is a sequence of about 20 amino acid residues from a virus that is recognized by a protease (2A peptidases) endogenous to the cell. The 2A peptide was identified among picornaviruses, a typical example of which is the Foot-and Mouth disease virus (Robertson BH, et. al., J Virol 1985, 54:651-660). 2A-like sequences have also been found in Picornaviridae like equine rhinitis A virus, as well as unrelated viruses such as porcine teschovirus-1 and the insect *Thosea asigna* virus (TaV). In such viruses, multiple proteins are derived from a large polyprotein encoded by an open reading frame. The 2A peptide mediates the co-translational cleavage of this polyprotein at a single site that forms the junction between the virus capsid and replication polyprotein

domains. The 2A sequences contain the consensus motif D-V/I-E-X-N-P-G-P (SEQ ID NO: 1235). These sequences are thought to act co-translationally, preventing the formation of a normal peptide bond between the glycine and last proline, resulting in the ribosome skipping of the next codon (Donnelly ML et al. (2001). *J Gen Virol,* 82:1013-1025). After cleavage, the short peptide remains fused to the C -terminus of the protein upstream of the cleavage site, while the proline is added to the N-terminus of the protein downstream of the cleavage site. Of the 2A peptides identified to date, four have been widely used namely FMDV 2A (abbreviated herein as F2A); equine rhinitis A virus (ERAV) 2A (E2A); porcine teschovirus-1 2A (P2A) and *Thoseaasigna* virus 2A (T2A). In some embodiments, the 2A peptide sequences useful in the present invention are selected from SEQ ID NO.8-11 of International Patent Publication WO2010042490, the contents of which are incorporated by reference in its entirety.

[00299] As a non-limiting example, the P2A cleavable peptide may be GATNFSLLKQAGDVEENPGP (SEQ ID NO: 925; encoded by SEQ ID NO: 926).

[00300] The linkers of the present invention may also be non-peptide linkers. For example, alkyl linkers such as ----NH----(CH_2) a-C(O)----, wherein a=2-20 can be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2, phenyl, etc.

[00301] In some aspects, the linker may be an artificial linker from U.S. Pat. NOs.: 4,946,778; 5, 525, 491; 5,856,456; and International patent publication NOs.: WO2012/083424; the contents of each of which are incorporated herein by reference in their entirety.

[00302] In some embodiments, linkers of the present invention, include without limitation, any of those taught in Table 11 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

[00303] In one embodiment, the linker may be a spacer region of one or more nucleotides. Non-limiting examples of spacers are TCTAGATAATACGACTCACTAGAGATCC (SEQ ID NO: 927), TATGGCCACAACCATG (SEQ ID NO: 928), AATCTAGATAATACGACTCACTAGAGATCC (SEQ ID NO: 929), GCTTGCCACAACCCACAAGGAGACGACCTTCC (SEQ ID NO: 1000), TCGCGAATG, or TCGCGA.

[00304] In one embodiment, the linker may be a BamHI site. As a non-limiting example, the BamHI site has the amino acid sequence GS and/or the DNA sequence GGATCC.

Embedded stimulus, signals and other regulatory features

[00305] In some embodiments, the effector module of the present invention may further comprise one or more microRNAs, microRNA binding sites, promotors and tunable elements. In one embodiment, microRNA may be used in support of the creation of tunable biocircuits. Each aspect or tuned modality may bring to the effector module or biocircuit a differentially tuned feature. For example, a destabilizing domain may alter cleavage sites or dimerization properties or half-life of the payload, and the inclusion of one or more microRNA or microRNA binding site may impart cellular detargeting or trafficking features. Consequently, the present invention embraces biocircuits which are multifactorial in their tenability. Such biocircuits and effector modules may be engineered to contain one, two, three, four or more tuned features.

[00306] In some embodiments, micro RNA sequences of the present invention, include without limitation, any of those taught in Table 13 of copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

[00307] In some embodiments, compositions of the invention may include optional proteasome adaptors. As used herein, the term "proteasome adaptor" refers to any nucleotide/ amino acid sequence that targets the appended payload for degradation. In some aspects, the adaptors target the payload for degradation directly thereby circumventing the need for ubiquitination reactions. Proteasome adaptors may be used in conjunction with destabilizing domains to reduce the basal expression of the payload. Exemplary proteasome adaptors include the UbL domain of Rad23 or hHR23b, HPV E7 which binds to both the target protein Rb and the S4 subunit of the proteasome with high affinity, which allows direct proteasome targeting, bypassing the ubiquitination machinery; the protein gankyrin which binds to Rb and the proteasome subunit S6.

Polynucleotides

[00308] The term “polynucleotide” or “nucleic acid molecule” in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides, e.g., linked nucleosides. These polymers are often referred to as polynucleotides. Exemplary nucleic acids or polynucleotides of the invention include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β- D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2′-amino-LNA having a 2′-amino functionalization, and 2′-amino- α-LNA having a 2′-amino functionalization) or hybrids thereof.

[00309] In some embodiments, polynucleotides of the invention may be a messenger RNA (mRNA) or any nucleic acid molecule and may or may not be chemically modified. In one aspect, the nucleic acid molecule is a mRNA. As used herein, the term "messenger RNA (mRNA)" refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro*, *in vivo*, *in situ* or *ex vivo*.

[00310] Traditionally, the basic components of an mRNA molecule include at least a coding region, a 5′UTR, a 3′UTR, a 5′ cap and a poly-A tail. Building on this wild type modular structure, the present invention expands the scope of functionality of traditional mRNA molecules by providing payload constructs which maintain a modular organization, but which comprise one or more structural and/or chemical modifications or alterations which impart useful properties to the polynucleotide, for example tenability of function. As used herein, a "structural" feature or modification is one in which two or more linked nucleosides are inserted, deleted, duplicated, inverted or randomized in a polynucleotide without significant chemical modification to the nucleosides themselves. Because chemical bonds will necessarily be broken and reformed to effect a structural modification, structural modifications are of a chemical nature and hence are chemical modifications. However, structural modifications will result in a different sequence of nucleotides. For example, the polynucleotide "ATCG" may be chemically modified to "AT-5meC-G". The same polynucleotide may be structurally modified from "ATCG" to "ATCCCG". Here, the dinucleotide "CC" has been inserted, resulting in a structural modification to the polynucleotide.

[00311] In some embodiments, polynucleotides of the present invention may harbor 5'UTR sequences which play a role in translation initiation. 5'UTR sequences may include features such as Kozak sequences which are commonly known to be involved in the process by which the ribosome initiates translation of genes, Kozak sequences have the consensus XCCR(A/G) CCAUG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG) and X is any nucleotide. In one embodiment, the Kozak sequence is ACCGCC. By engineering the features that are typically found in abundantly expressed genes of target cells or tissues, the stability and protein production of the polynucleotides of the invention can be enhanced.

[00312] Further provided are polynucleotides, which may contain an internal ribosome entry site (IRES) which play an important role in initiating protein synthesis in the absence of 5' cap structure in the polynucleotide. An IRES may act as the sole ribosome binding site, or may serve as one of the multiple binding sites. Polynucleotides of the invention containing more than one

functional ribosome binding site may encode several peptides or polypeptides that are translated independently by the ribosomes giving rise to bicistronic and/or multicistronic nucleic acid molecules.

[00313] In some embodiments, polynucleotides encoding biocircuits, effector modules, SREs and payloads of interest such as immunotherapeutic agents may include from about 30 to about 100,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to 70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000 nucleotides). In some aspects, polynucleotides of the invention may include more than 10,000 nucleotides.

[00314] Regions of the polynucleotides which encode certain features such as cleavage sites, linkers, trafficking signals, tags or other features may range independently from 10-1,000 nucleotides in length (e.g., greater than 20, 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, and 900 nucleotides or at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, and 1,000 nucleotides).

[00315] In some embodiments, polynucleotides of the present invention may further comprise embedded regulatory moieties such as microRNA binding sites within the 3′UTR of nucleic acid molecules which when bind to microRNA molecules, down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. Conversely, for the purposes of the polynucleotides of the present invention, microRNA binding sites can be engineered out of (i.e. removed from) sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, miR-142 and miR-146 binding sites may be removed to improve protein expression in the immune cells. In some embodiments, any of the encoded

payloads may be may be regulated by an SRE and then combined with one or more regulatory sequences to generate a dual or multi-tuned effector module or biocircuit system.

[00316] In some embodiments, polynucleotides of the present invention may encode fragments, variants, derivatives of polypeptides of the inventions. In some aspects, the variant sequence may keep the same or a similar activity. Alternatively, the variant may have an altered activity (e.g., increased or decreased) relative to the start sequence. Generally, variants of a particular polynucleotide or polypeptide of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen et al., Gapped BLAST and PSI-BLAST: a new generation of protein database search programs, *Nucleic Acids Res.*, 1997, 25:3389-3402.)

[00317] In some embodiments, polynucleotides of the present invention may be modified. As used herein, the terms "modified", or as appropriate, "modification" refers to chemical modification with respect to A, G, U (T in DNA) or C nucleotides. Modifications may be on the nucleoside base and/or sugar portion of the nucleosides which comprise the polynucleotide. In some embodiments, multiple modifications are included in the modified nucleic acid or in one or more individual nucleoside or nucleotide. For example, modifications to a nucleoside may include one or more modifications to the nucleobase and the sugar. Modifications to the polynucleotides of the present invention may include any of those taught in, for example, International Publication NO: WO2013052523, the contents of which are incorporated herein by reference in its entirety.

[00318] As described herein "nucleoside" is defined as a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). As described herein, "nucleotide" is defined as a nucleoside including a phosphate group.

[00319] In some embodiments, the modification may be on the internucleoside linkage (e.g., phosphate backbone). Herein, in the context of the polynucleotide backbone, the phrases "phosphate" and "phosphodiester" are used interchangeably. Backbone phosphate groups can be modified by replacing one or more of the oxygen atoms with a different substituent. Further, the modified nucleosides and nucleotides can include the wholesale replacement of an unmodified phosphate moiety with another internucleoside linkage. Examples of modified phosphate groups include, but are not limited to, phosphorothioate, phosphoroselenates, boranophosphates,

boranophosphate esters, hydrogen phosphonates, phosphoramidates, phosphorodiamidates, alkyl or aryl phosphonates, and phosphotriesters. Phosphorodithioates have both non-linking oxygens replaced by sulfur. The phosphate linker can also be modified by the replacement of a linking oxygen with nitrogen (bridged phosphoramidates), sulfur (bridged phosphorothioates), and carbon (bridged methylene-phosphonates). Other modifications which may be used are taught in, for example, International Application NO: WO2013052523, the contents of which are incorporated herein by reference in their entirety.

[00320] Chemical modifications and/or substitution of the nucleotides or nucleobases of the polynucleotides of the invention which are useful in the present invention include any modified substitutes known in the art, for example, (±)1-(2-Hydroxypropyl)pseudouridine TP, (2R)-1-(2-Hydroxypropyl)pseudouridine TP, 1-(4-Methoxy-phenyl)pseudo-UTP,,2′-O-dimethyladenosine, 1,2′-O-dimethylguanosine, 1,2′-O-dimethylinosine, 1-Hexyl-pseudo-UTP, 1-Homoallylpseudouridine TP, 1-Hydroxymethylpseudouridine TP, 1-iso-propyl-pseudo-UTP, 1-Me-2-thio-pseudo-UTP, 1-Me-4-thio-pseudo-UTP, 1-Me-alpha-thio-pseudo-UTP, 1-Me-GTP, 2'-Amino-2'-deoxy-ATP, 2'-Amino-2'-deoxy-CTP, 2'-Amino-2'-deoxy-GTP, 2'-Amino-2'-deoxy-UTP, 2'-Azido-2'-deoxy-ATP, tubercidine, under modified hydroxywybutosine, uridine 5-oxyacetic acid, uridine 5-oxyacetic acid methyl ester, wybutosine, wyosine, xanthine, Xanthosine-5'-TP, xylo-adenosine, zebularine, α-thio-adenosine, α-thio-cytidine, α-thio-guanosine, and/or α-thio-uridine.

[00321] Polynucleotides of the present invention may comprise one or more of the modifications taught herein. Different sugar modifications, base modifications, nucleotide modifications, and/or internucleoside linkages (e.g., backbone structures) may exist at various positions in the polynucleotide of the invention. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a polynucleotide such that the function of the polynucleotide is not substantially decreased. A modification may also be a 5′ or 3′ terminal modification. The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e. any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%,

from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%).

[00322] In some embodiments, one or more codons of the polynucleotides of the present invention may be replaced with other codons encoding the native amino acid sequence to tune the expression of the SREs, through a process referred to as codon selection. Since mRNA codon, and tRNA anticodon pools tend to vary among organisms, cell types, sub cellular locations and over time, the codon selection described herein is a spatiotemporal (ST) codon selection.

[00323] In some embodiments of the invention, certain polynucleotide features may be codon optimized. Codon optimization refers to a process of modifying a nucleic acid sequence for enhanced expression in the host cell by replacing at least 1, 2, 3, 4, 5, 10, 15, 20, 25, 50 or more codons of the native sequence with codons that are most frequently used in the genes of that host cell while maintaining the native amino acid sequence. Codon usage may be measured using the Codon Adaptation Index (CAI) which measures the deviation of a coding polynucleotide sequence from a reference gene set. Codon usage tables are available at the Codon Usage Database (http://www.kazusa.or.jp/codon/) and the CAI can be calculated by EMBOSS CAI program (http://emboss.sourceforge.net/). Codon optimization methods are known in the art and may be useful in efforts to achieve one or more of several goals. These goals include to match codon frequencies in target and host organisms to ensure proper folding, bias nucleotide content to alter stability or reduce secondary structures, minimize tandem repeat codons or base runs that may impair gene construction or expression, customize transcriptional and translational control regions, insert or remove protein signaling sequences, remove/add post translation modification sites in encoded protein (e.g. glycosylation sites), add, remove or shuffle protein domains, insert or delete restriction sites, modify ribosome binding sites and degradation sites, to adjust translational rates to allow the various domains of the protein to fold properly, or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art, and non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park CA), OptimumGene (GenScript, Piscataway, NJ), algorithms such as but not limited to, DNAWorks v3.2.3 and/or proprietary methods. In one embodiment, a polynucleotide sequence or portion thereof is codon optimized using optimization algorithms. Codon options for each amino acid are well-known in the art as are various species table for optimizing for expression in that particular species.

[00324] In some embodiments of the invention, certain polynucleotide features may be codon optimized. For example, a preferred region for codon optimization may be upstream (5') or downstream (3') to a region which encodes a polypeptide. These regions may be incorporated into the polynucleotide before and/or after codon optimization of the payload encoding region or open reading frame (ORF).

[00325] After optimization (if desired), the polynucleotide components are reconstituted and transformed into a vector such as, but not limited to, plasmids, viruses, cosmids, and artificial chromosomes.

[00326] Spatiotemporal codon selection may impact the expression of the polynucleotides of the invention, since codon composition determines the rate of translation of the mRNA species and its stability. For example, tRNA anticodons to optimized codons are abundant, and thus translation may be enhanced. In contrast, tRNA anticodons to less common codons are fewer and thus translation may proceed at a slower rate. Presnyak et al. have shown that the stability of an mRNA species is dependent on the codon content, and higher stability and thus higher protein expression may be achieved by utilizing optimized codons (Presnyak et al. (2015) Cell 160, 1111–1124; the contents of which are incorporated herein by reference in their entirety). Thus, in some embodiments, ST codon selection may include the selection of optimized codons to enhance the expression of the SRES, effector modules and biocircuits of the invention. In other embodiments, spatiotemporal codon selection may involve the selection of codons that are less commonly used in the genes of the host cell to decrease the expression of the compositions of the invention. The ratio of optimized codons to codons less commonly used in the genes of the host cell may also be varied to tune expression.

[00327] In some embodiments, certain regions of the polynucleotide may be preferred for codon selection. For example, a preferred region for codon selection may be upstream (5') or downstream (3') to a region which encodes a polypeptide. These regions may be incorporated into the polynucleotide before and/or after codon selection of the payload encoding region or open reading frame (ORF).

[00328] The stop codon of the polynucleotides of the present invention may be modified to include sequences and motifs to alter the expression levels of the SREs, payloads and effector modules of the present invention. Such sequences may be incorporated to induce stop codon readthrough, wherein the stop codon may specify amino acids e.g. selenocysteine or pyrrolysine. In other instances, stop codons may be skipped altogether to resume translation through an alternate open reading frame. Stop codon read through may be utilized to tune the expression of components of the effector modules at a specific ratio (e.g.as dictated by the stop codon context).

Examples of preferred stop codon motifs include UGAN, UAAN, and UAGN, where N is either C or U. Polynucleotide modifications and manipulations can be accomplished by methods known in the art such as, but not limited to, site directed mutagenesis and recombinant technology. The resulting modified molecules may then be tested for activity using *in vitro* or *in vivo* assays such as those described herein or any other suitable screening assay known in the art.

[00329] In some embodiments, polynucleotides of the invention may comprise two or more effector module sequences, or two or more payloads of interest sequences, which are in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times. In these patterns, each letter, A, B, or C represent a different effector module component.

[00330] In yet another embodiment, polynucleotides of the invention may comprise two or more effector module component sequences with each component having one or more SRE sequences (DD sequences), or two or more payload sequences. As a non-limiting example, the sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times in each of the regions. As another non-limiting example, the sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times across the entire polynucleotide. In these patterns, each letter, A, B, or C represent a different sequence or component.

[00331] According to the present invention, polynucleotides encoding distinct biocircuits, effector modules, SREs and payload constructs may be linked together through the 3′-end using nucleotides which are modified at the 3′-terminus. Chemical conjugation may be used to control the stoichiometry of delivery into cells. Polynucleotides can be designed to be conjugated to other polynucleotides, dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG, $(MPEG)_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases, proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell, hormones and hormone receptors, non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, or a drug. As non-limiting examples, they may be conjugates with other immune conjugates.

[00332] In some embodiments, the compositions of the polynucleotides of the invention may generated by combining the various components of the effector modules using the Gibson assembly method. The Gibson assembly reaction consists of three isothermal reactions, each relying on a different enzymatic activity including a 5' exonuclease which generates long overhangs, a polymerase which fills in the gaps of the annealed single strand regions and a DNA ligase which seals the nicks of the annealed and filled-in gaps. Polymerase chain reactions are performed prior to Gibson assembly which may be used to generate PCR products with overlapping sequence. These methods can be repeated sequentially, to assemble larger and larger molecules. For example, the method can comprise repeating a method as above to join a second set of two or more DNA molecules of interest to one another, and then repeating the method again to join the first and second set DNA molecules of interest, and so on. At any stage during these multiple rounds of assembly, the assembled DNA can be amplified by transforming it into a suitable microorganism, or it can be amplified in vitro (e.g., with PCR).

[00333] In some embodiments, polynucleotides of the present invention may encode a fusion polypeptide comprising a destabilizing domain (DD) and at least one immunotherapeutic agent taught herein. The DD domain may be a FKBP mutant encoded by nucleotide sequence of SEQ ID NO: 684-686, 688-691, 987-989, 994, 1013, and/or 1028, an ecDHFR mutant encoded by nucleotide sequence of SEQ ID NO: 687, 692, 772, 798, 814-815, 988, 991, and/or 993, hDHFR mutant encoded by nucleotide sequence of SEQ ID NO: 693-700, 773, 852-857 and/or 934-980, and/or 995-998.

[00334] In some embodiments, the polynucleotides of the invention may encode effector modules comprising the CD19 CAR as the payload comprising the nucleotide sequence of SEQ ID NO: 701-715 and/or 1019-1042, or IL12 as the payload comprising the nucleotide sequence of SEQ ID NO. 774-782, or IL15 as the payload comprising the nucleotide sequence of SEQ ID NO: 749, 799-800, and/or 1055-1056, or IL15/IL15Ra fusion polypeptide as the payload comprising the nucleotide sequence of SEQ ID NO: 816-821, 1086-1089, 1091-1095, 1098-1111, 1120, and/or 1123.

Cells

[00335] In accordance with the present invention, cells genetically modified to express at least one biocircuit, SRE (e. g, DD), effector module and immunotherapeutic agent of the invention, are provided. Cells of the invention may include, without limitation, immune cells, stem cells and tumor cells. In some embodiments, immune cells are immune effector cells, including, but not limiting to, T cells such as $CD8^+$ T cells and $CD4^+$ T cells (e.g., Th1, Th2, Th17, Foxp3+ cells), memory T cells such as T memory stem cells, central T memory cells, and effector

memory T cells, terminally differentiated effector T cells, natural killer (NK) cells, NK T cells, tumor infiltrating lymphocytes (TILs), cytotoxic T lymphocytes (CTLs), regulatory T cells (Tregs), and dendritic cells (DCs), other immune cells that can elicit an effector function, or the mixture thereof. T cells may be Tαβ cells and Tγδ cells. In some embodiments, stem cells may be from human embryonic stem cells, mesenchymal stem cells, and neural stem cells. In some embodiments, T cells may be depleted endogenous T cell receptors (See US Pat. NOs.: 9, 273, 283; 9, 181, 527; and 9,028, 812; the contents of each of which are incorporated herein by reference in their entirety).

[00336] In some embodiments, cells of the invention may be autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

[00337] In some embodiments, cells of the invention may be mammalian cells, particularly human cells. Cells of the invention may be primary cells or immortalized cell lines.

[00338] In some embodiments, cells of the invention may include expansion factors as payload to trigger proliferation and expansion of the cells. Exemplary payloads include RAS such as KRAS, NRAS, RRAS, RRAS2, MRAS, ERAS, and HRAS, DIRAS such as DIRAS1, DIRAS2, and DIRAS3, NKIRAS such as NKIRAS1, and NKIRAS2, RAL such as RALA, and RALB, RAP such as RAP1A, RAP1B, RAP2A, RAP2B, and RAP2C, RASD such as RASD1, and RASD2, RASL such as RASL10A, RASL10B, RASL11A, RASL11B, and RASL12, REM such as REM1, and REM2, GEM, RERG, RERGL, and RRAD.

[00339] Engineered immune cells can be accomplished by transducing a cell compositions with a polypeptide of a biocircuit, an effector module, a SRE and/or a payload of interest (i.e., immunotherapeutic agent), or a polynucleotide encoding said polypeptide, or a vector comprising said polynucleotide. The vector may be a viral vector such as a lentiviral vector, a gamma-retroviral vector, a recombinant AAV, an adenoviral vector and an oncolytic viral vector. In other aspects, non-viral vectors for example, nanoparticles and liposomes may also be used. In some embodiments, immune cells of the invention are genetically modified to express at least one immunotherapeutic agent of the invention which is tunable using a stimulus. In some examples, two, three or more immunotherapeutic agents constructed in the same biocircuit and effector module are introduced into a cell. In other examples, two, three, or more biocircuits, effector modules, each of which comprises an immunotherapeutic agent, may be introduced into a cell.

[00340] In some embodiments, immune cells of the invention may be T cells modified to express an antigen-specific T cell receptor (TCR), or an antigen specific chimeric antigen receptor (CAR) taught herein (known as CAR T cells). Accordingly, at least one polynucleotide

encoding a CAR system (or a TCR) described herein, or a vector comprising the polynucleotide is introduced into a T cell. The T cell expressing the CAR or TCR binds to a specific antigen via the extracellular targeting moiety of the CAR or TCR, thereby a signal via the intracellular signaling domain (s) is transmitted into the T cell, and as a result, the T cell is activated. The activated CAR T cell changes its behavior including release of a cytotoxic cytokine (e.g., a tumor necrosis factor, and lymphotoxin, etc.), improvement of a cell proliferation rate, change in a cell surface molecule, or the like. Such changes cause destruction of a target cell expressing the antigen recognized by the CAR or TCR. In addition, release of a cytokine or change in a cell surface molecule stimulates other immune cells, for example, a B cell, a dendritic cell, a NK cell, and a macrophage.

[00341] The CAR introduced into a T cell may be a first-generation CAR including only the intracellular signaling domain from TCR CD3zeta, or a second-generation CAR including the intracellular signaling domain from TCR CD3zeta and a costimulatory signaling domain, or a third-generation CAR including the intracellular signaling domain from TCR CD3zeta and two or more costimulatory signaling domains, or a split CAR system, or an on/off switch CAR system. In one example, the expression of the CAR or TCR is controlled by a destabilizing domain (DD) such as a hDHFR mutant, in the effector module of the invention. The presence or absence of hDHFR binding ligand such as TMP is used to tune the CAR or TCR expression in transduced T cells or NK cells.

[00342] In some embodiments, CAR T cells of the invention may be further modified to express another one, two, three or more immunotherapeutic agents. The immunotherapeutic agents may be another CAR or TCR specific to a different target molecule; a cytokine such as IL2, IL12, IL15 and IL18, or a cytokine receptor such as IL15Ra; a chimeric switch receptor that converts an inhibitory signal to a stimulatory signal; a homing receptor that guides adoptively transferred cells to a target site such as the tumor tissue; an agent that optimizes the metabolism of the immune cell; or a safety switch gene (e.g., a suicide gene) that kills activated T cells when a severe event is observed after adoptive cell transfer or when the transferred immune cells are no-longer needed. These molecules may be included in the same effector module or in separate effector modules.

[00343] In one embodiment, the CAR T cell (including TCR T cell) of the invention may be an "armed" CAR T cell which is transformed with an effector module comprising a CAR and an effector module comprising a cytokine. The inducible or constitutively secrete active cytokines further armor CAR T cells to improve efficacy and persistence. In this context, such CAR T cell is also referred to as "armored CAR T cell". The "armor" molecule may be selected based on the

tumor microenvironment and other elements of the innate and adaptive immune systems. In some embodiments, the molecule may be a stimulatory factor such as IL2, IL12, IL15, IL18, type I IFN, CD40L and 4-1BBL which have been shown to further enhance CAR T cell efficacy and persistence in the face of a hostile tumor microenvironment via different mechanisms (Yeku et al., *Biochem Soc Trans*., 2016, 44(2): 412-418).

[00344] In some aspects, the armed CAR T cell of the invention is modified to express a CD19 CAR and IL12. Such T cells, after CAR mediated activation in the tumor, release inducible IL12 which augments T-cell activation and attracts and activates innate immune cells to eliminate CD19-negative cancer cells.

[00345] In one embodiment, T cells of the invention may be modified to express an effector module comprising a CAR and an effector module comprising a suicide gene.

[00346] In one embodiment, the CAR T cell (including TCR T cell) of the invention may be transformed with effector modules comprising a cytokine and a safety switch gene (e.g., suicide gene). The suicide gene may be an inducible caspase such as caspase 9 which induces apoptosis, when activated by an extracellular stimulus of a biocircuit system. Such induced apoptosis eliminates transferred cell as required to decrease the risk of direct toxicity and uncontrolled cell proliferation.

[00347] In some embodiments, immune cells of the invention may be NK cells modified to express an antigen-specific T cell receptor (TCR), or an antigen specific chimeric antigen receptor (CAR) taught herein.

[00348] Natural killer (NK) cells are members of the innate lymphoid cell family and characterized in humans by expression of the phenotypic marker CD56 (neural cell adhesion molecule) in the absence of CD3 (T-cell co-receptor). NK cells are potent effector cells of the innate immune system which mediate cytotoxic attack without the requirement of prior antigen priming, forming the first line of defense against diseases including cancer malignancies and viral infection.

[00349] Several pre-clinical and clinical trials have demonstrated that adoptive transfer of NK cells is a promising treatment approach against cancers such as acute myeloid leukemia (Ruggeri et al., *Science*; 2002, 295: 2097–2100; and Geller et al., *Immunotherapy*, 2011, 3: 1445-1459). Adoptive transfer of NK cells expressing CAR such as DAP12-Based Activating CAR revealed improved eradication of tumor cells (Topfer et al., *J Immunol*. 2015; 194:3201–3212). NK cell engineered to express a CS-1 specific CAR also displayed enhanced cytolysis and interferon-γ (IFN-γ) production in multiple myeloma (Chu et al., *Leukemia*, 2014, 28(4): 917-927).

[00350] NK cell activation is characterized by an array of receptors with activating and inhibitory functions. The important activation receptors on NK cells include CD94/NKG2C and NKG2D (the C-type lectin-like receptors), and the natural cytotoxicity receptors (NCR) NKp30, NKp44 and NKp46, which recognize ligands on tumor cells or virally infected cells. NK cell inhibition is essentially mediated by interactions of the polymorphic inhibitory killer cell immunoglobulin-like receptors (KIRs) with their cognate human–leukocyte–antigen (HLA) ligands via the alpha-1 helix of the HLA molecule. The balance between signals that are generated from activating receptors and inhibitory receptors mainly determines the immediate cytotoxic activation.

[00351] NK cells may be isolated from peripheral blood mononuclear cells (PBMCs), or derived from human embryonic stem (ES) cells and induced pluripotent stem cells (iPSCs). The primary NK cells isolated from PBMCs may be further expanded for adoptive immunotherapy. Strategies and protocols useful for the expansion of NK cells may include interleukin 2 (IL2) stimulation and the use of autologous feeder cells, or the use of genetically modified allogeneic feeder cells. In some aspects, NK cells can be selectively expanded with a combination of stimulating ligands including IL15, IL21, IL2, 41BBL, IL12, IL18, MICA, 2B4, LFA-1, and BCM1/SLAMF2 (e.g., US patent publication NO: US20150190471).

[00352] Immune cells expressing effector modules comprising a CAR and/or other immunotherapeutic agents can be used as cancer immunotherapy. The immunotherapy comprises the cells expressing a CAR and/or other immunotherapeutic agents as an active ingredient, and may further comprise a suitable excipient. Examples of the excipient may include the aforementioned pharmaceutically acceptable excipients, including various cell culture media, and isotonic sodium chloride.

[00353] In some embodiments, cells of the present invention may be dendritic cells that are genetically modified to express the compositions of the invention. Such cells may be used as cancer vaccines.

Methods of CD19 antibody development and characterization

[00354] In some embodiments, the present invention provides methods of producing CD19 antibodies, antibody fragments or variants. Such methods may include the steps of: (1) preparing a composition with CD19, (2) contacting a library of antibodies or antibody fragments or variable with the composition, and (3) identifying one or more CD19 antibodies. Also, provided herein are methods for identifying FMC63-distinct CD19 antibodies, antibody fragments or variable.

[00355] In some embodiments, the present invention provides methods of identifying CD19 scFvs. Such methods may involve screening phagemid libraries for CD19 scFvs. Phagemid libraries expressing recombinant scFvs associated with the surface of bacteria or bacteriophages are useful in the present inventions. Phagemid libraries may be generated by PCR implication of the polynucleotides encoding the heavy chain and the kappa light chain of the immunoglobulin IgM and infecting Cre recombinase positive bacteria with the vectors containing the PCR products at a high multiplicity of infection (MOI). The high MOI results in bacteria containing multiple phagemids, each of which encodes a different VH and VL genes, which can be recombined by the Cre recombinase. The resulting library that may be generated by recombination is approximately 10^8 unique scFvs. In some instances, libraries of CD19 scFvs formatted into chimeric antigen receptor constructs may be screened to identify CD19scFvs useful in the present invention.

[00356] In some embodiments, scFvs immunologically specific to CD19 may be identified using cells that ectopically express full length, a fragment or a portion of CD19. Cell lines with low endogenous CD19 expression may be selected for ectopic expression. In some embodiments, the CD19 may be a naturally occurring isoform of human CD19.

[00357] In some embodiments, fusion proteins comprising the extracellular domains of CD19 (i.e. exon 1- exon 4) fused to the Fc region of human IgG1 (CD19sIg) are utilized to identify CD19 specific scFvs. Such fusion proteins have been described by Oliveira et al (2013) Journal of Translational Medicine 11:23; the contents of which are incorporated herein by reference in their entirety.

[00358] Also, provided herein are methods to identify FMC63-distinct scFvs, which include scFvs that are immunologically specific to and bind to an epitope of the CD19 antigen that is different or unlike the epitope of CD19 antigen that is bound by FMC63. In some embodiments, FMC63-distinct scFvs are identified by screening the scFv library with a complex consisting of human CD19 bound to FMC63. The CD19 of Rhesus macaque *(Macaca mulatta)* herein referred to as Rhesus CD19, bears 88% homology to the human CD19. Despite this high degree of homology, the Rhesus CD19 is not recognized by FMC63, indicating that the FMC63 epitope is in the region of human CD19 that is non-homologous to Rhesus CD19. Thus, in some embodiments, Rhesus CD19 may be used to screen scFv libraries for FMC63-distinct scFvs. Mutations in the region of Rhesus CD19 that is non-homologous to the human CD19 have been previously utilized to identify residues of human CD19 that confer binding to FMC63 (Sommermeyer et al. (2017) Leukemia Feb 16. doi: 10.1038/leu.2017.57). In some embodiments, the mutational analysis described by Sommermeyer et al. may be utilized to

design human CD19 mutants that are unable to bind to FMC63. Such mutants may include human CD19 (H218R, A237D, M243V, E244D, P250T) and human CD19 (H218R, A237D) and may be utilized to screen scFv libraries for FMC63-distinct scFvs. Sotillo et al have identified a splice variant of human CD19 lacking exon 2 in cancer patients (Sotillo et al. (2015) Cancer Discov. 2015 Dec;5(12):1282-95). The splice variant lacking exon 2 is not recognized by FMC63 and may also be used to screen scFv libraries for FMC63-distinct scFvs.

[00359] CD19 IgG fusion molecules generated by fusing the Fc region of human IgG1 with the human CD19-complete extracellular domains, i.e., exons 1-4 (CD19sIgG1-4) or extracellular domains lacking exon 2, i.e., exons 1, 3 and 4 (CD19sIgG1,3,4) may also be utilized to screen scFv libraries for FMC63-distinct scFvs.

[00360] CD19 proteins, variants and mutants useful in the invention are provided in Table 14.

Table 14: CD19 proteins, variants and mutants

Description	Sequence	SEQ ID NO
Human CD19, Isoform 1 (NCBI Reference No. NP_001171569.1)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLK GTSDGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIW LFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGE LFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVW AKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLS CGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARD MWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITA RPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQR ALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLP TPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSR SPPGVGPEEEEGEGYEEPDSEEDSEFYENDSNLGQDQLSQ DGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQPVAR TMDFLSPHGSAWDPSREATSLAGSQSYEDMRGILYAAPQ LRSIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGGRM GTWSTR	858
Human CD19, Isoform 2 (NCBI Reference No. NP_001761.3)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLK GTSDGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIW LFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGE LFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVW AKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLS CGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARD MWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITA RPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQR ALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLP TPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSR SPPGVGPEEEEGEGYEEPDSEEDSEFYENDSNLGQDQLSQ DGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQPVAR TMDFLSPHGSAWDPSREATSLGSQSYEDMRGILYAAPQLR SIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGGRMGT WSTR	859
Rhesus CD19 (Uniprot ID: F7F486)	MPPPCLLFFLLFLTPMEVRPQEPLVVKVEEGDNAVLQCLE GTSDGPTQQLVWCRDSPFEPFLNLSLGLPGMGIRMGPLGI WLLIFNVSNQTGGFYLCQPGLPSEKAWQPGWTVSVEGSG ELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLNSSQLYV WAKDRPEMWEGEPVCGPPRDSLNQSLSQDLTMAPGSTL WLSCGVPPDSVSRGPLSWTHVRPKGPKSSLLSLELKDDRP	860

	DRDMWVVDTGLLLTRATAQDAGKYYCHRGNWTKSFYL EITARPALWHWLLRIGGWKVPAVTLTYLIFCLCSLVGILQ LQRALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNV LSLPTPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQVDGA VGSRSPPGAGPEEEEGEGYEEPDSEEGSEFYENDSNFGQD QLSQDGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQ PVARTMDFLSPHGSAWDPSREATSLGSQSYEDMRGLLYA APQLRTIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGG RMGTWSAR	
Human CD19 (H218R, A237D, M243V, E244D, P250T)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLK GTSDGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIW LFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGE LFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVW AKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLS CGVPPDSVSRGPLSWTHVRPKGPKSLLSLELKDDRPDRD MWVVDTGLLLTRATAQDAGKYYCHRGNLTMSFHLEITA RPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQR ALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLP TPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSR SPPGVGPEEEEGEGYEEPDSEEDSEFYENDSNLGQDQLSQ DGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQPVAR TMDFLSPHGSAWDPSREATSLAGSQSYEDMRGILYAAPQ LRSIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGGRM GTWSTR	861
Human CD19 (H218R, A237D)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLK GTSDGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIW LFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGE LFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVW AKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLS CGVPPDSVSRGPLSWTHVRPKGPKSLLSLELKDDRPDRD MWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITA RPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGILHLQR ALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLP TPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSR SPPGVGPEEEEGEGYEEPDSEEDSEFYENDSNLGQDQLSQ DGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQPVAR TMDFLSPHGSAWDPSREATSLAGSQSYEDMRGILYAAPQ LRSIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGGRM GTWSTR	862
Human CD19 (Delta exon 2)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEGELFRWNVSDL GGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWE GEPPCLPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVS RGPLSWTHVHPKGPKSLLSLELKDDRPARDMWVMETGL LLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLL RTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKRKR MTDPTRRFFKVTPPPGSGPQNQYGNVLSLPTPTSGLGRAQ RWAAGLGGTAPSYGNPSSDVQADGALGSRSPPGVGPEEE EGEGYEEPDSEEDSEFYENDSNLGQDQLSQDGSGYENPED EPLGPEDEDSFSNAESYENEDEELTQPVARTMDFLSPHGS AWDPSREATSLGSQSYEDMRGILYAAPQLRSIRGQPGPNH EEDADSYENMDNPDGPDPAWGGGGRMGTWSTR	863
Human CD19 (Exon 1-4)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLK GTSDGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIW LFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGE LFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVW AKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLS CGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARD MWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITA RP	864

Human CD19 (Exon 1,3,4)	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEGELFRWNVSDL GGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWE GEPPCLPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVS RGPLSWTHVHPKGPKSLLSLELKDDRPARDMWVMETGL LLPRATAQDAGKYYCHRGNLTMSFHLEITARP	865

III. PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

[00361] The present invention further provides pharmaceutical compositions comprising one or more biocircuits, effector modules, SREs (e.g., DDs), stimuli and payloads of interest (i.e., immunotherapeutic agents), vectors, cells and other components of the invention, and optionally at least one pharmaceutically acceptable excipient or inert ingredient.

[00362] As used herein the term "pharmaceutical composition" refers to a preparation of biocircuits, SREs, stimuli and payloads of interest (i.e., immunotherapeutic agents), other components, vectors, cells and described herein, or pharmaceutically acceptable salts thereof, optionally with other chemical components such as physiologically suitable carriers and excipients. The pharmaceutical compositions of the invention comprise an effective amount of one or more active compositions of the invention. The preparation of a pharmaceutical composition that contains at least one composition of the present invention and/or an additional active ingredient will be known to those skilled in the art in light of the present disclosure, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, incorporated herein by reference.

[00363] The term "excipient" or "inert ingredient" refers to an inactive substance added to a pharmaceutical composition and formulation to further facilitate administration of an active ingredient. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to any one or more biocircuits, effector modules, SREs, stimuli and payloads of interest (i.e., immunotherapeutic agents), other components, vectors, and cells to be delivered as described herein. The phrases "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate.

[00364] In some embodiments, pharmaceutical compositions and formulations are administered to humans, human patients or subjects. Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, non-human mammals, including

agricultural animals such as cattle, horses, chickens and pigs, domestic animals such as cats, dogs, or research animals such as mice, rats, rabbits, dogs and non-human primates. It will be understood that, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biological Standards.

[00365] A pharmaceutical composition and formulation in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[00366] The compositions of the present invention may be formulated in any manner suitable for delivery. The formulation may be, but is not limited to, nanoparticles, poly (lactic-co-glycolic acid) (PLGA) microspheres, lipidoids, lipoplex, liposome, polymers, carbohydrates (including simple sugars), cationic lipids and combinations thereof.

[00367] In one embodiment, the formulation is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG and PEGylated lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA and DODMA.

[00368] For polynucleotides of the invention, the formulation may be selected from any of those taught, for example, in International Application PCT/US2012/069610, the contents of which are incorporated herein by reference in its entirety.

[00369] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient or inert ingredient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1 and 100, e.g., between 0.5 and 50, between 1-30, between 5-80, at least 80 (w/w) active ingredient.

[00370] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or

prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of compositions of the present invention, "effective against" for example a cancer, indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of cancer.

[00371] A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10 in a measurable parameter of disease, and preferably at least 20, 30, 40, 50 or more can be indicative of effective treatment. Efficacy for a given composition or formulation of the present invention can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant change is observed.

IV. APPLICATIONS

[00372] In one aspect of the present invention, methods for reducing a tumor volume or burden are provided. The methods comprise administering a pharmaceutically effective amount of a pharmaceutical composition comprising at least one biocircuit system, effector module, DD, and/or payload of interest (i.e., an immunotherapeutic agent), at least one vector, or cells to a subject having a tumor. The biocircuit system and effector module having any immunotherapeutic agent as described herein may be in forms of a polypeptide, or a polynucleotide such as mRNA, or a viral vector comprising the polynucleotide, or a cell modified to express the biocircuit, effector module, DD, and payload of interest (i.e., immunotherapeutic agent).

[00373] In another aspect of the present invention, methods for inducing an anti-tumor immune response in a subject are provided. The methods comprise administering a pharmaceutically effective amount of a pharmaceutical composition comprising at least one biocircuit system, effector module, DD, and/or payload of interest (i.e., an immunotherapeutic agent), at least one vector, or cells to a subject having a tumor. The biocircuit and effector module having any immunotherapeutic agent as described herein may be in forms of a polypeptide, or a polynucleotide such as mRNA, or a viral vector comprising the polynucleotide, or a cell modified to express the biocircuit, effector module, DD, and payload of interest (i.e., immunotherapeutic agent).

[00374] The methods, according to the present invention, may be adoptive cell transfer (ACT) using genetically engineered cells such as immune effector cells of the invention, cancer vaccines comprising biocircuit systems, effector modules, DDs, payloads of interest (i.e., immunotherapeutic agents) of the invention, or compositions that manipulate the tumor immunosuppressive microenvironment, or the combination thereof. These treatments may be further employed with other cancer treatment such as chemotherapy and radiotherapy.

1. Adoptive cell transfer (adoptive immunotherapy)

[00375] In some embodiments, cells which are genetically modified to express at least one biocircuit system, effector module, DD, and/or payload of interest (immunotherapeutic agent) may be used for adoptive cell therapy (ACT). As used herein, Adoptive cell transfer refers to the administration of immune cells (from autologous, allogenic or genetically modified hosts) with direct anticancer activity. ACT has shown promise in clinical application against malignant and infectious disease. For example, T cells genetically engineered to recognize CD19 have been used to treat follicular B cell lymphoma (Kochenderfer et al., *Blood*, 2010, 116:4099-4102; and Kochenderfer and Rosenberg, *Nat Rev Clin Oncol.*, 2013, 10(5): 267-276) and ACT using autologous lymphocytes genetically-modified to express anti-tumor T cell receptors has been used to treat metastatic melanoma (Rosenberg and Dudley, *Curr. Opin. Immunol.* 2009, 21: 233-240).

[00376] According to the present invention, the biocircuits and systems may be used in the development and implementation of cell therapies such as adoptive cell therapy. Certain effector modules useful in cell therapy are given in Figures 7-12. The biocircuits, their components, effector modules and their SREs and payloads may be used in cell therapies to effect CAR therapies, in the manipulation or regulation of TILs, in allogeneic cell therapy, in combination T cell therapy with other treatment lines (e.g. radiation, cytokines), to encode engineered TCRs, or modified TCRs, or to enhance T cells other than TCRs (e.g. by introducing cytokine genes, genes for the checkpoint inhibitors PD1, CTLA4).

[00377] Provided herein are methods for use in adoptive cell therapy. The methods involve preconditioning a subject in need thereof, modulating immune cells with SRE, biocircuits and compositions of the present invention, administering to a subject, engineered immune cells expressing compositions of the invention and the successful engraftment of engineered cells within the subject.

[00378] In some embodiments, SREs, biocircuits and compositions of the present invention may be used to minimize preconditioning regimens associated with adoptive cell therapy. As used herein "preconditioning" refers to any therapeutic regimen administered to a subject to

improve the outcome of adoptive cell therapy. Preconditioning strategies include, but are not limited to total body irradiation and/or lymphodepleting chemotherapy. Adoptive therapy clinical trials without preconditioning have failed to demonstrate any clinical benefit, indicating its importance in ACT. Yet, preconditioning is associated with significant toxicity and limits the subject cohort that is suitable for ACT. In some instances, immune cells for ACT may be engineered to express cytokines such as IL12 and IL15 as payload using SREs of the present invention to reduce the need for preconditioning (Pengram et al. (2012) Blood 119 (18): 4133-41; the contents of which are incorporated by reference in their entirety).

[00379] In some embodiments, immune cells for ACT may be dendritic cells, T cells such as $CD8^+$ T cells and $CD4^+$ T cells, natural killer (NK) cells, NK T cells, Cytotoxic T lymphocytes (CTLs), tumor infiltrating lymphocytes (TILs), lymphokine activated killer (LAK) cells, memory T cells, regulatory T cells (Tregs), helper T cells, cytokine-induced killer (CIK) cells, and any combination thereof. In other embodiments, immune stimulatory cells for ACT may be generated from embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC). In some embodiments, autologous or allogeneic immune cells are used for ACT.

[00380] In some embodiments, cells used for ACT may be T cells engineered to express CARs comprising an antigen-binding domain specific to an antigen on tumor cells of interest. In other embodiments, cells used for ACT may be NK cells engineered to express CARs comprising an antigen-binding domain specific to an antigen on tumor cells of interest. In addition to adoptive transfer of genetically modified T cells (e.g., CAR T cells) for immunotherapy, alternate types of CAR-expressing leukocytes, either alone, or in combination with CAR T cells may be used for adoptive immunotherapy. In one example, a mixture of T cells and NK cells may be used for ACT. The expression level of CARs in T cells and NK cells, according to the present invention, is tuned and controlled by a small molecule that binds to the DD(s) operably linked to the CAR in the effector module.

[00381] In some embodiments, the CARs of the present invention may be placed under the transcriptional control of the T cell receptor alpha constant (TRAC) locus in the T cells to achieve uniform CAR expression while enhancing T cell potency. The TRAC locus may be disrupted using the CRISPR/Cas 9, zinc finger nucleases (ZFNs), TALENs followed by the insertion of the CAR construct. Methods of engineering CAR constructs directed to the TRAC locus are described in Eyquem J. et al (2017) Nature.543(7643):113-117 (the contents of which are incorporated herein by reference in their entirety).

[00382] In some embodiments, NK cells engineered to express the present compositions may be used for ACT. NK cell activation induces perforin/granzyme-dependent apoptosis in target cells.

NK cell activation also induces cytokine secretion such as IFN-γ, TNF-α and GM-CSF. These cytokines enhance the phagocytic function of macrophages and their antimicrobial activity, and augment the adaptive immune response via up-regulation of antigen presentation by antigen presenting cells such as dendritic cells (DCs) (Reviewed by Vivier et al., *Nat. Immunol.*, 2008, 9(5): 503-510).

[00383] Other examples of genetic modification may include the introduction of chimeric antigen receptors (CARs) and the down-regulation of inhibitory NK cell receptors such as NKG2A.

[00384] NK cells may also be genetically reprogrammed to circumvent NK cell inhibitory signals upon interaction with tumor cells. For example, using CRISPR, ZFN, or TALEN to genetically modify NK cells to silence their inhibitory receptors may enhance the anti-tumor capacity of NK cells.

[00385] Immune cells can be isolated and expanded *ex vivo* using a variety of methods known in the art. For example, methods of isolating and expanding cytotoxic T cells are described in U.S. Pat. NOs. 6,805,861 and 6,531, 451; US Patent Publication No.: US20160348072A1 and International Patent Publication NO: WO2016168595A1; the contents of each of which are incorporated herein by reference in their entirety. Isolation and expansion of NK cells is described in US Patent Publication NO.: US20150152387A1, U.S. Patent NO.: 7,435, 596; and Oyer, J.L. (2016). Cytotherapy.18(5):653-63; the contents of each of which are incorporated by reference herein in its entirety. Specifically, human primary NK cells may be expanded in the presence of feeder cells e.g. a myeloid cell line that has been genetically modified to express membrane bound IL15, IL21, IL12 and 4-1BBL.

[00386] In some instances, sub populations of immune cells may be enriched for ACT. Methods for immune cell enrichment are taught in International Patent Publication NO.: WO2015039100A1. In another example, T cells positive for B and T lymphocyte attenuator marker BTLA) may be used to enrich for T cells that are anti-cancer reactive as described in U.S. Pat. NO.: 9,512,401 (the content of each of which are incorporated herein by reference in their entirety).

[00387] In some embodiments, immune cells for ACT may be depleted of select sub populations to enhance T cell expansion. For example, immune cells may be depleted of Foxp3+ T lymphocytes to minimize the ant-tumor immune response using methods taught in US Patent Publication NO.: US 20160298081A1; the contents of which are incorporated by reference herein in their entirety.

[00388] In some embodiments, activation and expansion of T cells for ACT is achieved antigenic stimulation of a transiently expressed Chimeric Antigen Receptor (CAR) on the cell surface. Such activation methods are taught in International Patent NO.: WO2017015427, the content of which are incorporated herein by reference in their entirety.

[00389] In some embodiments, immune cells may be activated by antigens associated with antigen presenting cells (APCs). In some embodiments, the APCs may be dendritic cells, macrophages or B cells that antigen specific or nonspecific. The APCs may autologous or homologous in their organ. In some embodiments, the APCs may be artificial antigen presenting cells (aAPCs) such as cell based aAPCs or acellular aAPCs. Cell based aAPCs are may be selected from either genetically modified allogeneic cells such as human erythroleukemia cells or xenogeneic cells such as murine fibroblasts and Drosophila cells. Alternatively, the APCs maybe be acellular wherein the antigens or costimulatory domains are presented on synthetic surfaces such as latex beads, polystyrene beads, lipid vesicles or exosomes.

[00390] In some embodiments, cells of the invention, specifically T cells may be expanded using artificial cell platforms. In one embodiment, the mature T cells may be generated using artificial thymic organoids (ATOs) described by Seet CS et al. 2017. *Nat Methods*. 14, 521–530 (the contents of which are incorporated herein by reference in their entirety). ATOs are based on a stromal cell line expressing delta like canonical notch ligand (DLL1). In this method, stromal cells are aggregated with hematopoietic stem and progenitor cells by centrifugation and deployed on a cell culture insert at the air–fluid interface to generate organoid cultures. ATO-derived T cells exhibit naive phenotypes, a diverse T cell receptor (TCR) repertoire and TCR-dependent function.

[00391] In some embodiments, adoptive cell therapy is carried out by autologous transfer, wherein the cells are derived from a subject in need of a treatment and the cells, following isolation and processing are administered to the same subject. In other instances, ACT may involve allogenic transfer wherein the cells are isolated and/or prepared from a donor subject other than the recipient subject who ultimately receives cell therapy. The donor and recipient subject may be genetically identical, or similar or may express the same HLA class or subtype.

[00392] In some embodiments, the multiple immunotherapeutic agents introduced into the immune cells for ACT (e.g., T cells and NK cells) may be controlled by the same biocircuit system. In one example, a cytokine such as IL12 and a CAR construct such as CD19 CAR are linked to the same hDHFR destabilizing domain. The expression of IL12 and CD19 CAR is tuned using TMP simultaneously. In other embodiments, the multiple immunotherapeutic agents introduced into the immune cells for ACT (e.g., T cells and NK cells) may be controlled by

different biocircuit systems. In one example, a cytokine such as IL12 and a CAR construct such as CD19 CAR are linked to different DDs in two separate effector modules, thereby can be tuned separately using different stimuli. In another example, a suicide gene and a CAR construct may be linked to two separate effector modules.

[00393] Following genetic modulation using SREs, biocircuits and compositions of the invention, cells are administered to the subject in need thereof. Methods for administration of cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions. For example, adoptive T cell therapy methods are described, e.g., in US Patent Application Publication No. 2003/0170238 to Gruenberg et al; US Patent No. 4,690,915 to Rosenberg; Rosenberg (2011) Nat Rev Clin Oncol. 8(10):577-85). See, e.g., Themeli et al. (2013) Nat Biotechnol. 31(10): 928-933; Tsukahara et al. (2013) Biochem Biophys Res Commun 438(1): 84-9; Davila et al. (2013) PLoS ONE 8(4): e61338; the contents of each of which are incorporated herein by reference in their entirety.

[00394] In some embodiments, immune cells for ACT may be modified to express one or more immunotherapeutic agents which facilitate immune cells activation, infiltration, expansion, survival and anti-tumor functions. The immunotherapeutic agents may be a second CAR or TCR specific to a different target molecule; a cytokine or a cytokine receptor; a chimeric switch receptor that converts an inhibitory signal to a stimulatory signal; a homing receptor that guides adoptively transferred cells to a target site such as the tumor tissue; an agent that optimizes the metabolism of the immune cell; or a safety switch gene (e.g., a suicide gene) that kills activated T cells when a severe event is observed after adoptive cell transfer or when the transferred immune cells are no-longer needed.

[00395] In some embodiments, immune cells used for adoptive cell transfer can be genetically manipulated to improve their persistence, cytotoxicity, tumor targeting capacity, and ability to home to disease sites *in vivo*, with the overall aim of further improving upon their capacity to kill tumors in cancer patients. One example is to introduce effector modules of the invention comprising cytokines such as gamma-cytokines (IL2 and IL15) into immune cells to promote immune cell proliferation and survival. Transduction of cytokine genes (e.g., gamma-cytokines IL2 and IL15) into cells will be able to propagate immune cells without addition of exogenous cytokines and cytokine expressing NK cells have enhanced tumor cytotoxicity.

[00396] In some embodiments, biocircuits, their components, SREs or effector modules may be utilized to prevent T cell exhaustion. As used herein, "T cell exhaustion" refers to the stepwise and progressive loss of T cell function caused by chronic T cell activation. T cell exhaustion is a major factor limiting the efficacy of antiviral and antitumor immunotherapies. Exhausted T cells

have low proliferative and cytokine producing capabilities concurrent with high rates of apoptosis and high surface expression of multiple inhibitory receptors. T cell activation leading to exhaustion may occur either in the presence or absence of the antigen.

[00397] In some embodiments, the biocircuits, and their components may be utilized to prevent T cell exhaustion in the context of Chimeric Antigen Receptor - T cell therapy (CAR-T). In this context, exhaustion in some instances, may be caused by the oligomerization of the scFvs of the CAR on the cell surface which leads to continuous activation of the intracellular domains of the CAR. As a non-limiting example, CARs of the present invention may include scFvs that are unable to oligomerize. As another non-limiting example, CARs that are rapidly internalized and re-expressed following antigen exposure may also be selected to prevent chronic scFv oligomerization on cell surface. In one embodiment, the framework region of the scFvs may be modified to prevent constitutive CAR signaling (Long et al. 2014. Cancer Research. 74(19) S1; the contents of which are incorporated by reference in their entirety). Tunable biocircuit systems of the present invention may also be used to regulate the surface expression of the CAR on the T cell surface to prevent chronic T cell activation. The CARs of the invention may also be engineered to minimize exhaustion. As a non-limiting example, the 41-BB signaling domain may be incorporated into CAR design to ameliorate T cell exhaustion. In some embodiments, any of the strategies disclosed by Long H A et al. may be utilized to prevent exhaustion (Long A H et al. (2015) Nature Medicine 21, 581–590; the contents of which are incorporated herein by reference in their entirety).

[00398] In some embodiments, the tunable nature of the biocircuits of the present invention may be utilized to reverse human T cell exhaustion observed with tonic CAR signaling. Reversibly silencing the biological activity of adoptively transferred cells using compositions of the present invention may be used to reverse tonic signaling which, in turn, may reinvigorate the T cells. Reversal of exhaustion may be measured by the downregulation of multiple inhibitory receptors associated with exhaustion.

[00399] In some embodiments, T cell metabolic pathways may be modified to diminish the susceptibility of T cells to exhaustion. Metabolic pathways may include, but are not limited to glycolysis, urea cycle, citric acid cycle, beta oxidation, fatty acid biosynthesis, pentose phosphate pathway, nucleotide biosynthesis, and glycogen metabolic pathways. As a non-limiting example, payloads that reduce the rate of glycolysis may be utilized to restrict or prevent T cell exhaustion (Long et al. Journal for Immunotherapy of Cancer 2013, 1(Suppl 1): P21; the contents of which are incorporated by reference in their entirety). In one embodiment, T cells of the present

invention may be used in combination with inhibitors of glycolysis such as 2-deoxyglucose, and rapamycin.

[00400] In some embodiments, effector modules of the present invention, useful for immunotherapy may be placed under the transcriptional control of the T cell receptor alpha locus constant (TRAC) locus in the T cells. Eyquem et al. have shown that expression of the CAR from the TRAC locus prevents T cell exhaustion and the accelerated differentiation of T cells caused by excessive T cell activation (Eyquem J. et al (2017) Nature.543(7643):113-117; the contents of which are incorporated herein by reference in their entirety).

[00401] In some embodiments, payloads of the invention may be used in conjunction with antibodies or fragments that target T cell surface markers associated with T cell exhaustion. T-cell surface markers associated with T cell exhaustion that may be used include, but are not limited to, CTLA-1, PD-1, TGIT, LAG-3, 2B4, BTLA, TIM3, VISTA, and CD96.

[00402] In one embodiment, the payload of the invention may be a CD276 CAR (with CD28, 4-IBB, and CD3 zeta intracellular domains), that does not show an upregulation of the markers associated with early T cell exhaustion (see International patent publication No. WO2017044699; the contents of which are incorporated by reference in their entirety).

[00403] In some embodiments, the compositions of the present invention may be utilized to alter TIL (tumor infiltrating lymphocyte) populations in a subject. In one embodiment, any of the payloads described herein may be utilized to change the ratio of CD4 positive cells to CD8 positive populations. In some embodiments, TILs may be sorted ex vivo and engineered to express any of the cytokines described herein. Payloads of the invention may be used to expand CD4 and/or CD8 populations of TILs to enhance TIL mediated immune response.

2. Cancer vaccines

[00404] In some embodiments, biocircuits, effector modules, payloads of interest (immunotherapeutic agents), vectors, cells and compositions of the present invention may be used in conjunction with cancer vaccines.

[00405] In some embodiments, cancer vaccine may comprise peptides and/or proteins derived from tumor associated antigen (TAA). Such strategies may be utilized to evoke an immune response in a subject, which in some instances may be a cytotoxic T lymphocyte (CTL) response. Peptides used for cancer vaccines may also modified to match the mutation profile of a subject. For example, EGFR derived peptides with mutations matched to the mutations found in the subject in need of therapy have been successfully used in patients with lung cancer (Li F et al. (2016) Oncoimmunology. Oct 7;5(12): e1238539; the contents of which are incorporated herein by reference in their entirety).

[00406] In one embodiment, cancer vaccines of the present invention may superagonist altered peptide ligands (APL) derived from TAAs. These are mutant peptide ligands deviate from the native peptide sequence by one or more amino acids, which activate specific CTL clones more effectively than native epitopes. These alterations may allow the peptide to bind better to the restricting Class I MHC molecule or interact more favorably with the TCR of a given tumor-specific CTL subset. APLs may be selected using methods taught in US Patent Publication NO.: US20160317633A1, the contents of which are incorporated herein by reference in their entirety.

3. Combination treatments

[00407] In some embodiments, it is desirable to combine compositions, vectors and cells of the invention for administration to a subject. Compositions of the invention comprising different immunotherapeutic agents may be used in combination for enhancement of immunotherapy.

[00408] In some embodiments, it is desirable to combine compositions of the invention with adjuvants, that can enhance the potency and longevity of antigen-specific immune responses. Adjuvants used as immunostimulants in combination therapy include biological molecules or delivery carriers that deliver antigens. As non-limiting examples, the compositions of the invention may be combined with biological adjuvants such as cytokines, Toll Like Receptors, bacterial toxins, and/or saponins. In other embodiments, the compositions of the present invention may be combined with delivery carriers. Exemplary delivery carriers include, polymer microspheres, immune stimulating complexes, emulsions (oil-in-water or water-in-oil), aluminum salts, liposomes or virosomes.

[00409] In some embodiments, immune effector cells modified to express biocircuits, effector modules, DDs and payloads of the invention may be combined with the biological adjuvants described herein. Dual regulation of CAR and cytokines and ligands to segregate the kinetic control of target-mediated activation from intrinsic cell T cell expansion. Such dual regulation also minimizes the need for pre-conditioning regimens in patients. As a non-limiting example, DD regulated CAR e.g. CD19 CAR may be combined with cytokines e.g. IL12 to enhance the anti-tumor efficacy of the CAR (Pegram H.J., et al. Tumor-targeted T cells modified to secrete IL12 eradicate systemic tumors without need for prior conditioning. Blood.2012;119:4133–41; the contents of each of which are incorporated herein by reference in their entirety). As another non-limiting example, Merchant et al. combined dendritic cell- based vaccinations with recombinant human IL7 to improve outcome in high-risk pediatric sarcomas patients (Merchant, M.S et. al. Adjuvant immunotherapy to Improve Outcome in High-Risk Pediatric Sarcomas. Clin Cancer Res. 2016. 22(13):3182-91; the contents of each of which are incorporated herein by reference in their entirety).

[00410] In some embodiments, immune effector cells modified to express one or more antigen-specific TCRs or CARs may be combined with compositions of the invention comprising immunotherapeutic agents that convert the immunosuppressive tumor microenvironment.

[00411] In one aspect, effector immune cells modified to express CARs specific to different target molecules on the same cell may be combined. In another aspect, different immune cells modified to express the same CAR construct such as NK cells and T cells may be used in combination for a tumor treatment, for instance, a T cell modified to express a CD19 CAR may be combined with a NK cell modified to express the same CD19 CAR to treat B cell malignancy.

[00412] In other embodiments, immune cells modified to express CARs may be combined with checkpoint blockade agents.

[00413] In some embodiments, immune effector cells modified to expressed biocircuits, effector modules, DDs and payloads of the invention may be combined with cancer vaccines of the invention.

[00414] In some embodiments, methods of the invention may include combination of the compositions of the invention with other agents effective in the treatment of cancers, infection diseases and other immunodeficient disorders, such as anti-cancer agents. As used herein, the term "anti-cancer agent" refers to any agent which is capable of negatively affecting cancer in a subject, for example, by killing cancer cells, inducing apoptosis in cancer cells, reducing the growth rate of cancer cells, reducing the incidence or number of metastases, reducing tumor size, inhibiting tumor growth, reducing the blood supply to a tumor or cancer cells, promoting an immune response against cancer cells or a tumor, preventing or inhibiting the progression of cancer, or increasing the lifespan of a subject with cancer.

[00415] In some embodiments, anti-cancer agent or therapy may be a chemotherapeutic agent, or radiotherapy, immunotherapeutic agent, surgery, or any other therapeutic agent which, in combination with the present invention, improves the therapeutic efficacy of treatment.

[00416] In one embodiment, an effector module comprising a CD19 CAR may be used in combination with amino pyrimidine derivatives such as the Burkit's tyrosine receptor kinase (BTK) inhibitor using methods taught in International Patent Application NO.: WO2016164580, the contents of which are incorporated herein by reference in their entirety.

[00417] In some embodiments, compositions of the present invention may be used in combination with immunotherapeutics other than the inventive therapy described herein, such as antibodies specific to some target molecules on the surface of a tumor cell.

[00418] Exemplary chemotherapies include, without limitation, Acivicin; Aclarubicin; Acodazole hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin;

Ametantrone acetate; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperrin, Sulindac, Curcumin, alkylating agents including: Nitrogen mustards such as mechlor-ethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas such as carmustine (BC U), lomustine (CCNU), and semustine (methyl-CC U); thylenimines/methylmelamine such as thriethylenemelamine (TEM), triethylene, thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC); antimetabolites including folic acid analogs such as methotrexate and trimetrexate, pyrrolidine analogs such as 5- fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'- difluorodeoxycytidine, purine analogs such as 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2- CdA); natural products including antimitotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorelbine, taxotere, estramustine, and estramustine phosphate; epipodophylotoxins such as etoposide and teniposide; antibiotics, such as actimomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycinC, and actinomycin; enzymes such as L-asparaginase, cytokines such as interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, TNF-beta and GM-CSF, anti-angiogenic factors, such as angiostatin and endostatin, inhibitors of FGF or VEGF such as soluble forms of receptors for angiogenic factors, including soluble VGF/VEGF receptors, platinum coordination complexes such as cisplatin and carboplatin, anthracenediones such as mitoxantrone, substituted urea such as hydroxyurea, methylhydrazine derivatives including N- methylhydrazine (MIFf) and procarbazine, adrenocortical suppressants such as mitotane (o,ρ'-DDD) and aminoglutethimide; hormones and antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide; progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate; estrogen such as diethylstilbestrol and ethinyl estradiol equivalents; antiestrogen such as tamoxifen; androgens including testosterone propionate and fluoxymesterone/equivalents; antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide; non-steroidal antiandrogens such as flutamide; kinase inhibitors, histone deacetylase inhibitors, methylation inhibitors, proteasome inhibitors, monoclonal antibodies, oxidants, anti-oxidants, telomerase inhibitors, BH3 mimetics, ubiquitin ligase inhibitors, stat inhibitors and receptor tyrosin kinase inhibitors such as imatinib mesylate (marketed as Gleevac or Glivac) and erlotinib (an EGF receptor inhibitor) now marketed as Tarveca; anti-virals such as oseltamivir phosphate, Amphotericin B, and palivizumab; Sdi 1

mimetics; Semustine; Senescence derived inhibitor 1; Sparfosic acid; Spicamycin D; Spiromustine; Splenopentin; Spongistatin 1; Squalamine; Stipiamide; Stromelysin inhibitors; Sulfinosine; Superactive vasoactive intestinal peptide antagonist; Velaresol; Veramine; Verdins; Verteporfin; Vinorelbine; Vinxaltine; Vitaxin; Vorozole; Zanoterone; Zeniplatin; Zilascorb; and Zinostatin stimalamer; PI3Kβ small-molecule inhibitor, GSK2636771; pan-PI3K inhibitor (BKM120); BRAF inhibitors. Vemurafenib (Zelboraf) and dabrafenib (Tafinlar); or any analog or derivative and variant of the foregoing.

[00419] Radiotherapeutic agents and factors include radiation and waves that induce DNA damage for example, γ-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions, radioisotopes, and the like. Therapy may be achieved by irradiating the localized tumor site with the above described forms of radiations. It is most likely that all of these factors effect a broad range of damage DNA, on the precursors of DNA, the replication and repair of DNA, and the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

[00420] In some embodiments, the chemotherapeutic agent may be an immunomodulatory agent such as lenalidomide (LEN). Recent studies have demonstrated that lenalidomide can enhance antitumor functions of CAR modified T cells (Otahal et al., *Oncoimmunology*, 2015, 5(4): e1115940). Some examples of anti-tumor antibodies include tocilizumab, siltuximab.

[00421] Other agents may be used in combination with compositions of the invention may also include, but not limited to, agents that affect the upregulation of cell surface receptors and their ligands such as Fas/Fas ligand, DR4 or DR5/TRAIL and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion such as focal adhesion kinase (FAKs) inhibitors and Lovastatin, or agents that increase the sensitivity of the hyper proliferative cells to apoptotic inducers such as the antibody C225.

[00422] The combinations may include administering the compositions of the invention and other agents at the same time or separately. Alternatively, the present immunotherapy may precede or follow the other agent/therapy by intervals ranging from minutes, days, weeks to months.

4. Diseases

[00423] Provided in the present invention is a method of reducing a tumor volume or burden in a subject in need, the method comprising introducing into the subject a composition of the invention.

[00424] The present invention also provides methods for treating a cancer in a subject, comprising administering to the subject an effective amount of an immune effector cell genetically modified to express at least one effector module of the invention.

Cancer

[00425] Various cancers may be treated with pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs or payloads of the present invention. As used herein, the term "cancer" refers to any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites and also refers to the pathological condition characterized by such malignant neoplastic growths. Cancers may be tumors or hematological malignancies, and include but are not limited to, all types of lymphomas/leukemias, carcinomas and sarcomas, such as those cancers or tumors found in the anus, bladder, bile duct, bone, brain, breast, cervix, colon/rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid and uterus.

[00426] Types of carcinomas which may be treated with the compositions of the present invention include, but are not limited to, papilloma/carcinoma, choriocarcinoma, endodermal sinus tumor, teratoma, adenoma/adenocarcinoma, melanoma, fibroma, lipoma, leiomyoma, rhabdomyoma, mesothelioma, angioma, osteoma, chondroma, glioma, lymphoma/leukemia, squamous cell carcinoma, small cell carcinoma, large cell undifferentiated carcinomas, basal cell carcinoma and sinonasal undifferentiated carcinoma.

[00427] Types of carcinomas which may be treated with the compositions of the present invention include, but are not limited to, soft tissue sarcoma such as alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, and Askin's tumor, Ewing's sarcoma (primitive neuroectodermal tumor), malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, and chondrosarcoma.

[00428] As a non-limiting example, the carcinoma which may be treated may be Acute granulocytic leukemia, Acute lymphocytic leukemia, Acute myelogenous leukemia, Adenocarcinoma, Adenosarcoma, Adrenal cancer, Adrenocortical carcinoma, Anal cancer, Anaplastic astrocytoma, Angiosarcoma, Appendix cancer, Astrocytoma, Basal cell carcinoma, B-Cell lymphoma), Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain cancer,

Brain stem glioma, Brain tumor, Breast cancer, Carcinoid tumors, Cervical cancer, Cholangiocarcinoma, Chondrosarcoma, Chronic lymphocytic leukemia, Chronic myelogenous leukemia, Colon cancer, Colorectal cancer, Craniopharyngioma, Cutaneous lymphoma, Cutaneous melanoma, Diffuse astrocytoma, Ductal carcinoma in situ, Endometrial cancer, Ependymoma, Epithelioid sarcoma, Esophageal cancer, Ewing sarcoma, Extrahepatic bile duct cancer, Eye cancer, Fallopian tube cancer, Fibrosarcoma, Gallbladder cancer, Gastric cancer, Gastrointestinal cancer, Gastrointestinal carcinoid cancer, Gastrointestinal stromal tumors, General, Germ cell tumor, Glioblastoma multiforme, Glioma, Hairy cell leukemia, Head and neck cancer, Hemangioendothelioma, Hodgkin lymphoma, Hodgkin's disease, Hodgkin's lymphoma, Hypopharyngeal cancer, Infiltrating ductal carcinoma, Infiltrating lobular carcinoma, Inflammatory breast cancer, Intestinal Cancer, Intrahepatic bile duct cancer, Invasive / infiltrating breast cancer, Islet cell cancer, Jaw cancer, Kaposi sarcoma, Kidney cancer, Laryngeal cancer, Leiomyosarcoma, Leptomeningeal metastases, Leukemia, Lip cancer, Liposarcoma, Liver cancer, Lobular carcinoma in situ, Low-grade astrocytoma, Lung cancer, Lymph node cancer, Lymphoma, Male breast cancer, Medullary carcinoma, Medulloblastoma, Melanoma, Meningioma, Merkel cell carcinoma, Mesenchymal chondrosarcoma, Mesenchymous, Mesothelioma, Metastatic breast cancer, Metastatic melanoma, Metastatic squamous neck cancer, Mixed gliomas, Mouth cancer, Mucinous carcinoma, Mucosal melanoma, Multiple myeloma, Nasal cavity cancer, Nasopharyngeal cancer, Neck cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma, Non-Hodgkin's lymphoma, Non-small cell lung cancer, Oat cell cancer, Ocular cancer, Ocular melanoma, Oligodendroglioma, Oral cancer, Oral cavity cancer, Oropharyngeal cancer, Osteogenic sarcoma, Osteosarcoma, Ovarian cancer, Ovarian epithelial cancer, Ovarian germ cell tumor, Ovarian primary peritoneal carcinoma, Ovarian sex cord stromal tumor, Paget's disease, Pancreatic cancer, Papillary carcinoma, Paranasal sinus cancer, Parathyroid cancer, Pelvic cancer, Penile cancer, Peripheral nerve cancer, Peritoneal cancer, Pharyngeal cancer, Pheochromocytoma, Pilocytic astrocytoma, Pineal region tumor, Pineoblastoma, Pituitary gland cancer, Primary central nervous system lymphoma, Prostate cancer, Rectal cancer, Renal cell cancer, Renal pelvis cancer, Rhabdomyosarcoma, Salivary gland cancer, Sarcoma, Sarcoma, bone, Sarcoma, soft tissue, Sarcoma, uterine, Sinus cancer, Skin cancer, Small cell lung cancer, Small intestine cancer, Soft tissue sarcoma, Spinal cancer, Spinal column cancer, Spinal cord cancer, Spinal tumor, Squamous cell carcinoma, Stomach cancer, Synovial sarcoma, T-cell lymphoma), Testicular cancer, Throat cancer, Thymoma / thymic carcinoma, Thyroid cancer, Tongue cancer, Tonsil cancer, Transitional cell cancer, Transitional cell cancer, Transitional cell cancer, Triple-

negative breast cancer, Tubal cancer, Tubular carcinoma, Ureteral cancer, Ureteral cancer, Urethral cancer, Uterine adenocarcinoma, Uterine cancer, Uterine sarcoma, Vaginal cancer, and Vulvar cancer.

Infectious diseases

[00429] In some embodiment, biocircuits of the invention may be used for the treatment of infectious diseases. Biocircuits of the invention may be introduced in cells suitable for adoptive cell transfer such as macrophages, dendritic cells, natural killer cells, and or T cells. Infectious diseases treated by the biocircuits of the invention may be diseases caused by viruses, bacteria, fungi, and/or parasites. IL15-IL15Ra payloads of the invention may be used to increase immune cell proliferation and/or persistence of the immune cells useful in treating infectious diseases.

[00430] "Infection diseases" herein refer to diseases caused by any pathogen or agent that infects mammalian cells, preferably human cells and causes a disease condition. Examples thereof include bacteria, yeast, fungi, protozoans, mycoplasma, viruses, prions, and parasites. Examples include those involved in (a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e-g-, an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenza virus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV); (b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella; (c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, parasitic diseases including but not limited to malaria, Pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection and prions that cause human disease such as Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), Gerstmann-Straüssler-Scheinker syndrome, Fatal Familial Insomnia and kuru.

5. Microbiome

[00431] Alterations in the composition of the microbiome may impact the action of anti-cancer therapies. A diverse community of symbiotic, commensal and pathogenic microorganisms exist in all environmentally exposed sites in the body and is herein referred to as the "Microbiome." Environmentally exposed sites of the body that may be inhabited by a microbiome include the skin, nasopharynx, the oral cavity, respiratory tract, gastrointestinal tract, and the reproductive tract.

[00432] In some embodiments, microbiome native or engineered with immunotherapeutic agents may be used to improve the efficacy of the anti-cancer immunotherapies. Methods of using microbiome to improve responsive to immunotherapeutic agents have been described by Sivan et al (Sivan A., et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015; 350:1084–9; the contents of which are incorporated herein by reference in their entirety). In one embodiment, protein, RNA and/or other biomolecules derived from the microbiome may be used as a payload to influence the efficacy of the anti-cancer immunotherapies.

6. Tools and agents for making therapeutics

[00433] Provided in the present invention are tools and agents that may be used in generating immunotherapeutics for reducing a tumor volume or burden in a subject in need. A considerable number of variables are involved in producing a therapeutic agent, such as structure of the payload, type of cells, method of gene transfers, method and time of ex vivo expansion, pre-conditioning and the amount and type of tumor burden in the subject. Such parameters may be optimized using tools and agents described herein.

Cell lines

[00434] The present disclosure provides a mammalian cell that has been genetically modified with the compositions of the invention. Suitable mammalian cells include primary cells and immortalized cell lines. Suitable mammalian cell lines include, but are not limited to Human embryonic kidney cell line 293, fibroblast cell line NIH 3T3, human colorectal carcinoma cell line HCT116, ovarian carcinoma cell line SKOV-3, immortalized T cell lines (e.g. Jurkat cells and SupT1 cells), lymphoma cell line Raji cells, NALM-6 cells, K562 cells, HeLa cells, PC12 cells, HL-60 cells, NK cell lines (e.g. NKL, NK92, NK962, and YTS), and the like. In some instances, the cell is not an immortalized cell line, but instead a cell obtained from an individual and is herein referred to as a primary cell. For example, the cell is a T lymphocyte obtained from an individual. Other examples include, but are not limited to cytotoxic cells, stem cells, peripheral blood mononuclear cells or progenitor cells obtained from an individual.

Tracking SREs, biocircuits and cell lines

[00435] In some embodiments, it may be desirable to track the compositions of the invention or the cells modified by the compositions of the invention. Tracking may be achieved by using reporter moieties, which, as used herein, refers to any protein capable of creating a detectable signal, in response to an input. Examples include alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase, β-glucuronidase, peroxidase, β-lactamase, catalytic antibodies, bioluminescent proteins e.g. luciferase, and fluorescent proteins such as Green fluorescent protein (GFP).

[00436] Reporter moieties may be used to monitor the response of the DD upon addition of the ligand corresponding to the DD. In other instances, reporter moieties may be used to track cell survival, persistence, cell growth, and/or localization *in vitro, in vivo, or ex vivo.*

[00437] In some embodiments, the preferred reporter moiety may be luciferase proteins. In one embodiment, the reporter moiety is the Renilla luciferase (SEQ ID NO. 866, encoded by nucleic acid sequence of SEQ ID NO. 867), or a firefly luciferase (SEQ ID NO. 868, encoded by nucleic acid sequence of SEQ ID NO. 869).

Animal models

[00438] The utility and efficacy of the compositions of the present invention may be tested *in vivo* animal models, preferably mouse models. Mouse models used to may be syngeneic mouse models wherein mouse cells are modified with compositions of the invention and tested in mice of the same genetic background. Examples include pMEL-1 and 4T1 mouse models. Alternatively, xenograft models where human cells such as tumor cells and immune cells are introduced into immunodeficient mice may also be utilized in such studies. Immunodeficient mice used may be CByJ.Cg-Foxn1^{nu}/J, B6;129S7-*Rag1*^{tm1Mom}/J, B6.129S7-*Rag1*^{tm1Mom}/J, B6.CB17-*Prkdc*^{scid}/SzJ, NOD.129S7(B6)-*Rag1*^{tm1Mom}/J, NOD.Cg-*Rag1*^{tm1Mom}*Prf1*^{tm1Sd}z/Sz, NOD.CB17-*Prkdc*^{scid}/SzJ, NOD.Cg-*Prkdc*^{scid}*B2m*^{tm1Unc}/J, NOD-*scid* IL2Rg^{null}, Nude (nu) mice, SCID mice, NOD mice, RAG1/RAG2 mice, NOD-Scid mice, IL2rg*null* mice, b2m*null* mice, NOD-*scid* IL2rγnull mice, NOD-*scid*-B2m*null* mice, beige mouse, and HLA transgenic mice.

Cellular assays

[00439] In some embodiments, the effectiveness of the compositions of the inventions as immunotherapeutic agents may be evaluated using cellular assays. Levels of expression and/or identity of the compositions of the invention may be determined according to any methods known in the art for identifying proteins and/or quantitating proteins levels. In some embodiments, such methods may include Western Blotting, flow cytometry, and immunoassays.

[00440] Provided herein are methods for functionally characterizing cells expressing SRE, biocircuits and compositions of the invention. In some embodiments, functional characterization is carried out in primary immune cells or immortalized immune cell lines and may be determined by expression of cell surface markers. Examples of cell surface markers for T cells include, but are not limited to, CD3, CD4, CD8, CD 14, CD20, CD11b, CD16, CD45 and HLA-DR, CD 69, CD28, CD44, IFNgamma. Markers for T cell exhaustion include PD1, TIM3, BTLA, CD160, 2B4, CD39, and LAG3. Examples of cell surface markers for antigen presenting cells include, but are not limited to, MHC class I, MHC Class II, CD40, CD45, B7-1, B7-2, IFN-γ receptor and IL2 receptor, ICAM-1 and/or Fcγ receptor. Examples of cell surface markers for dendritic cells include, but are not limited to, MHC class I, MHC Class II, B7-2, CD18, CD29, CD31, CD43, CD44, CD45, CD54, CD58, CD83, CD86, CMRF-44, CMRF-56, DCIR and/or Dectin-1 and the like; while in some cases also having the absence of CD2, CD3, CD4, CD8, CD14, CD15, CD16, CD 19, CD20, CD56, and/or CD57. Examples of cell surface markers for NK cells include, but are not limited to, CCL3, CCL4, CCL5, CCR4, CXCR4, CXCR3, NKG2D, CD71, CD69, CCR5, Phospho JAK/STAT, phospho ERK, phospho p38/ MAPK, phospho AKT, phospho STAT3, Granulysin, Granzyme B, Granzyme K, IL10, IL22, IFNg, LAP, Perforin, and TNFa.

V. DELIVERY MODALITIES AND/OR VECTORS

Vectors

[00441] The present invention also provides vectors that package polynucleotides of the invention encoding biocircuits, effector modules, SREs (DDs) and payload constructs, and combinations thereof. Vectors of the present invention may also be used to deliver the packaged polynucleotides to a cell, a local tissue site or a subject. These vectors may be of any kind, including DNA vectors, RNA vectors, plasmids, viral vectors and particles. Viral vector technology is well known and described in Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York). Viruses, which are useful as vectors include, but are not limited to lentiviral vectors, adenoviral vectors, adeno-associated viral (AAV) vectors, herpes simplex viral vectors, retroviral vectors, oncolytic viruses, and the like.

[00442] In general, vectors contain an origin of replication functional in at least one organism, a promoter sequence and convenient restriction endonuclease site, and one or more selectable markers e.g. a drug resistance gene.

[00443] As used herein a promoter is defined as a DNA sequence recognized by transcription machinery of the cell, required to initiate specific transcription of the polynucleotide sequence of

the present invention. Vectors can comprise native or non-native promoters operably linked to the polynucleotides of the invention. The promoters selected may be strong, weak, constitutive, inducible, tissue specific, development stage-specific, and/or organism specific. One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of polynucleotide sequence that is operatively linked to it. Another example of a preferred promoter is Elongation Growth Factor-1. Alpha (EF-1. alpha). Other constitutive promoters may also be used, including, but not limited to simian virus 40 (SV40), mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV), long terminal repeat (LTR), promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter as well as human gene promoters including, but not limited to the phosphoglycerate kinase (PGK) promoter, actin promoter, the myosin promoter, the hemoglobin promoter, the Ubiquitin C (Ubc) promoter, the human U6 small nuclear protein promoter and the creatine kinase promoter. In some instances, inducible promoters such as but not limited to metallothionine promoter, glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter may be used. In some embodiments, the promoter may be selected from the SEQ ID NO.: 716-718.

[00444] In some embodiments, the optimal promoter may be selected based on its ability to achieve minimal expression of the SREs and payloads of the invention in the absence of the ligand and detectable expression in the presence of the ligand.

[00445] Additional promoter elements e.g. enhancers may be used to regulate the frequency of transcriptional initiation. Such regions may be located 10-100 base pairs upstream or downstream of the start site. In some instances, two or more promoter elements may be used to cooperatively or independently activate transcription.

[00446] In some embodiments, the recombinant expression vector may comprise regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell into which the vector is to be introduced.

1. Lentiviral vectors

[00447] In some embodiments, lentiviral vectors/particles may be used as vehicles and delivery modalities. Lentiviruses are subgroup of the *Retroviridae* family of viruses, named because reverse transcription of viral RNA genomes to DNA is required before integration into the host genome. As such, the most important features of lentiviral vehicles/particles are the integration of their genetic material into the genome of a target/host cell. Some examples of lentivirus include the Human Immunodeficiency Viruses: HIV-1 and HIV-2, the Simian

Immunodeficiency Virus (SIV), feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), Jembrana Disease Virus (JDV), equine infectious anemia virus (EIAV), equine infectious anemia virus, visna-maedi and caprine arthritis encephalitis virus (CAEV).

[00448] Typically, lentiviral particles making up the gene delivery vehicle are replication defective on their own (also referred to as "self-inactivating"). Lentiviruses are able to infect both dividing and non-dividing cells by virtue of the entry mechanism through the intact host nuclear envelope (Naldini L et al., *Curr. Opin. Biotechnol*, 1998, 9: 457-463). Recombinant lentiviral vehicles/particles have been generated by multiply attenuating the HIV virulence genes, for example, the genes Env, Vif, Vpr, Vpu, Nef and Tat are deleted making the vector biologically safe. Correspondingly, lentiviral vehicles, for example, derived from HIV-1/HIV-2 can mediate the efficient delivery, integration and long-term expression of transgenes into non-dividing cells. As used herein, the term "recombinant" refers to a vector or other nucleic acid containing both lentiviral sequences and non-lentiviral retroviral sequences.

[00449] Lentiviral particles may be generated by co-expressing the virus packaging elements and the vector genome itself in a producer cell such as human HEK293T cells. These elements are usually provided in three (in second generation lentiviral systems) or four separate plasmids (in third generation lentiviral systems). The producer cells are co-transfected with plasmids that encode lentiviral components including the core (i.e. structural proteins) and enzymatic components of the virus, and the envelope protein(s) (referred to as the packaging systems), and a plasmid that encodes the genome including a foreign transgene, to be transferred to the target cell, the vehicle itself (also referred to as the transfer vector). In general, the plasmids or vectors are included in a producer cell line. The plasmids/vectors are introduced via transfection, transduction or infection into the producer cell line. Methods for transfection, transduction or infection are well known by those of skill in the art. As non-limiting example, the packaging and transfer constructs can be introduced into producer cell lines by calcium phosphate transfection, lipofection or electroporation, generally together with a dominant selectable marker, such as neo, DHFR, Gln synthetase or ADA, followed by selection in the presence of the appropriate drug and isolation of clones.

[00450] The producer cell produces recombinant viral particles that contain the foreign gene, for example, the effector module of the present invention. The recombinant viral particles are recovered from the culture media and titrated by standard methods used by those of skill in the art. The recombinant lentiviral vehicles can be used to infect target cells.

[00451] Cells that can be used to produce high-titer lentiviral particles may include, but are not limited to, HEK293T cells, 293G cells, STAR cells (Relander et al., *Mol. Ther.*, 2005, 11: 452-

459), FreeStyle™ 293 Expression System (ThermoFisher, Waltham, MA), and other HEK293T-based producer cell lines (e.g., Stewart et al., *Hum Gene Ther.* 2011, 22(3):357-369; Lee et al., *Biotechnol Bioeng*, 2012, 10996): 1551-1560; Throm et al., *Blood.* 2009, 113(21): 5104-5110; the contents of each of which are incorporated herein by reference in their entirety).

[00452] In some aspects, the envelope proteins may be heterologous envelop proteins from other viruses, such as the G protein of vesicular stomatitis virus (VSV G) or baculoviral gp64 envelop proteins. The VSV-G glycoprotein may especially be chosen among species classified in the vesiculovirus genus: *Carajas virus* (CJSV), *Chandipura virus* (CHPV), *Cocal virus* (COCV), *Isfahan virus* (ISFV), *Maraba virus* (MARAV), *Piry virus* (PIRYV), *Vesicular stomatitis Alagoas virus* (VSAV), *Vesicular stomatitis Indiana virus* (VSIV) *and Vesicular stomatitis New Jersey virus* (VSNJV) and/or stains provisionally classified in the vesiculovirus genus as *Grass carp rhabdovirus*, *BeAn 157575 virus* (BeAn 157575), *Boteke virus* (BTKV), *Calchaqui virus* (CQIV), *Eel virus American* (EVA), *Gray Lodge virus* (GLOV), *Jurona virus* (JURY), *Klamath virus* (KLAV), *Kwatta virus* (KWAV), *La Joya virus* (LJV), *Malpais Spring virus* (MSPV), *Mount Elgon bat virus* (MEBV), *Perinet virus* (PERV), *Pike fry rhabdovirus* (PFRV), *Porton virus* (PORV), *Radi virus* (RADIV), *Spring viremia of carp virus* (SVCV), *Tupaia virus* (TUPV), *Ulcerative disease rhabdovirus* (UDRV) and *Yug Bogdanovac virus* (YBV). The gp64 or other baculoviral env protein can be derived from *Autographa californica* nucleopolyhedrovirus (AcMNPV), *Anagrapha falcifera* nuclear polyhedrosis virus, *Bombyx mori* nuclear polyhedrosis virus, *Choristoneura fumiferana* nucleopolyhedrovirus, *Orgyia pseudotsugata* single capsid nuclear polyhedrosis virus, *Epiphyas postvittana* nucleopolyhedrovirus, *Hyphantria cunea* nucleopolyhedrovirus, *Galleria mellonella* nuclear polyhedrosis virus, Dhori virus, Thogoto virus, *Antheraea pemyi* nucleopolyhedrovirus or Batken virus.

[00453] Additional elements provided in lentiviral particles may comprise retroviral LTR (long-terminal repeat) at either 5' or 3' terminus, a retroviral export element, optionally a lentiviral reverse response element (RRE), a promoter or active portion thereof, and a locus control region (LCR) or active portion thereof. Other elements include central polypurine tract (cPPT) sequence to improve transduction efficiency in non-dividing cells, Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element (WPRE) which enhances the expression of the transgene, and increases titer. The effector module is linked to the vector.

[00454] Methods for generating recombinant lentiviral particles are discussed in the art, for example, U.S. Pat. NOs.: 8, 846, 385; 7,745, 179; 7,629,153; 7,575,924; 7,179, 903; and 6, 808, 905; the contents of each of which are incorporated herein by reference in their entirety.

[00455] Lentivirus vectors used may be selected from, but are not limited to pLVX, pLenti, pLenti6, pLJM1, FUGW, pWPXL, pWPI, pLenti CMV puro DEST, pLJM1-EGFP, pULTRA, pInducer20, pHIV-EGFP, pCW57.1, pTRPE, pELPS, pRRL, and pLionII.

[00456] Lentiviral vehicles known in the art may also be used (See, U.S. Pat. NOs. 9, 260, 725; 9,068,199; 9,023,646; 8,900,858; 8,748,169; 8,709,799; 8,420,104; 8,329,462; 8,076,106; 6,013,516; and 5,994,136; International Patent Publication NO.: WO2012079000; the contents of each of which are incorporated herein by reference in their entirety).

2. Retroviral vectors (γ-retroviral vectors)

[00457] In some embodiments, retroviral vectors may be used to package and deliver the biocircuits, biocircuit components, effector modules, SREs or payload constructs of the present invention. Retroviral vectors (RVs) allow the permanent integration of a transgene in target cells. In addition to lentiviral vectors based on complex HIV-1/2, retroviral vectors based on simple gamma-retroviruses have been widely used to deliver therapeutic genes and demonstrated clinically as one of the most efficient and powerful gene delivery systems capable of transducing a broad range of cell types. Example species of Gamma retroviruses include the murine leukemia viruses (MLVs) and the feline leukemia viruses (FeLV).

[00458] In some embodiments, gamma-retroviral vectors derived from a mammalian gamma-retrovirus such as murine leukemia viruses (MLVs), are recombinant. The MLV families of gamma retroviruses include the ecotropic, amphotropic, xenotropic and polytropic subfamilies. Ecotropic viruses are able to infect only murine cells using mCAT-1 receptor. Examples of ecotropic viruses are Moloney MLV and AKV. Amphotropic viruses infect murine, human and other species through the Pit-2 receptor. One example of an amphotropic virus is the 4070A virus. Xenotropic and polytropic viruses utilize the same (Xpr1) receptor, but differ in their species tropism. Xenotropic viruses such as NZB-9-1 infect human and other species but not murine species, whereas polytropic viruses such as focus-forming viruses (MCF) infect murine, human and other species.

[00459] Gamma-retroviral vectors may be produced in packaging cells by co-transfecting the cells with several plasmids including one encoding the retroviral structural and enzymatic (gag-pol) polyprotein, one encoding the envelope (env) protein, and one encoding the vector mRNA comprising polynucleotide encoding the compositions of the present invention that is to be packaged in newly formed viral particles.

[00460] In some aspects, the recombinant gamma-retroviral vectors are pseudotyped with envelope proteins from other viruses. Envelope glycoproteins are incorporated in the outer lipid layer of the viral particles which can increase/alter the cell tropism. Exemplary envelop proteins

include the gibbon ape leukemia virus envelope protein (GALV) or vesicular stomatitis virus G protein (VSV-G), or Simian endogenous retrovirus envelop protein, or Measles Virus H and F proteins, or Human immunodeficiency virus gp120 envelope protein, or cocal vesiculovirus envelop protein (See, e.g., U.S. application publication NO.: 2012/164118; the contents of which are incorporated herein by reference in its entirety). In other aspects, envelope glycoproteins may be genetically modified to incorporate targeting/binding ligands into gamma-retroviral vectors, binding ligands including, but not limited to, peptide ligands, single chain antibodies and growth factors (Waehler et al., *Nat. Rev. Genet.* 2007, 8(8):573–587; the contents of which are incorporated herein by reference in its entirety). These engineered glycoproteins can retarget vectors to cells expressing their corresponding target moieties. In other aspects, a "molecular bridge" may be introduced to direct vectors to specific cells. The molecular bridge has dual specificities: one end can recognize viral glycoproteins, and the other end can bind to the molecular determinant on the target cell. Such molecular bridges, for example ligand-receptor, avidin-biotin, and chemical conjugations, monoclonal antibodies and engineered fusogenic proteins, can direct the attachment of viral vectors to target cells for transduction (Yang et al., *Biotechnol. Bioeng.*, 2008, 101(2): 357-368; and Maetzig et al., *Viruses*, 2011, 3, 677-713; the contents of each of which are incorporated herein by reference in their entirety).

[00461] In some embodiments, the recombinant gamma-retroviral vectors are self-inactivating (SIN) gammaretroviral vectors. The vectors are replication incompetent. SIN vectors may harbor a deletion within the 3' U3 region initially comprising enhancer/promoter activity. Furthermore, the 5' U3 region may be replaced with strong promoters (needed in the packaging cell line) derived from Cytomegalovirus or RSV, or an internal promoter of choice, and/or an enhancer element. The choice of the internal promoters may be made according to specific requirements of gene expression needed for a particular purpose of the invention.

[00462] In some embodiments, polynucleotides encoding the biocircuit, biocircuit components, effector module, SRE are inserted within the recombinant viral genome. The other components of the viral mRNA of a recombinant gamma-retroviral vector may be modified by insertion or removal of naturally occurring sequences (e.g., insertion of an IRES, insertion of a heterologous polynucleotide encoding a polypeptide or inhibitory nucleic acid of interest, shuffling of a more effective promoter from a different retrovirus or virus in place of the wild-type promoter and the like). In some examples, the recombinant gamma-retroviral vectors may comprise modified packaging signal, and/or primer binding site (PBS), and/or 5'-enhancer/promoter elements in the U3-region of the 5'- long terminal repeat (LTR), and/or 3'-SIN elements modified in the U3-region of the 3'-LTR. These modifications may increase the titers and the ability of infection.

[00463] Gamma retroviral vectors suitable for delivering biocircuit components, effector modules, SREs or payload constructs of the present invention may be selected from those disclosed in U.S. Pat. NOs.: 8,828,718; 7,585,676; 7,351,585; U.S. application publication NO.: 2007/048285; PCT application publication NOs.: WO2010/113037; WO2014/121005; WO2015/056014; and EP Pat. NOs.: EP1757702; EP1757703 (the contents of each of which are incorporated herein by reference in their entirety).

3. Adeno-associated viral vectors (AAV)

[00464] In some embodiments, polynucleotides of present invention may be packaged into recombinant adeno-associated viral (rAAV) vectors. Such vectors or viral particles may be designed to utilize any of the known serotype capsids or combinations of serotype capsids. The serotype capsids may include capsids from any identified AAV serotypes and variants thereof, for example, AAV1, AAV2, AAV2G9, AAV3, AAV4, AAV4-4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 and AAVrh10.

[00465] In one embodiment, the AAV serotype may be or have a sequence as described in United States Publication No. US20030138772, herein incorporated by reference in its entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO: 5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10 (amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772) or variants thereof. Non-limiting examples of variants include SEQ ID NOs: 9, 27-45, 47-62, 66-69, 73-81, 84-94, 96, 97, 99, 101-113 of US20030138772, the contents of which are herein incorporated by reference in their entirety.

[00466] In one embodiment, the AAV serotype may have a sequence as described in Pulicherla et al. (*Molecular Therapy*, 2011, 19(6):1070-1078), U.S. Pat. NOs.: 6,156,303; 7,198,951; U.S. Patent Publication NOs.: US2015/0159173 and US2014/0359799; and International Patent Publication NOs.: WO1998/011244, WO2005/033321 and WO2014/14422; the contents of each of which are incorporated herein by reference in their entirety.

[00467] AAV vectors include not only single stranded vectors but self-complementary AAV vectors (scAAVs). scAAV vectors contain DNA which anneals together to form double stranded vector genome. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[00468] The rAAV vectors may be manufactured by standard methods in the art such as by triple transfection, in sf9 insect cells or in suspension cell cultures of human cells such as HEK293 cells.

[00469] The biocircuits, biocircuit components, effector modules, SREs or payload constructs may be encoded in one or more viral genomes to be packaged in the AAV capsids taught herein.

[00470] Such vectors or viral genomes may also include, in addition to at least one or two ITRs (inverted terminal repeats), certain regulatory elements necessary for expression from the vector or viral genome. Such regulatory elements are well known in the art and include for example promoters, introns, spacers, stuffer sequences, and the like.

[00471] In some embodiments, more than one effector module or SRE (e.g. DD) may be encoded in a viral genome.

4. Oncolytic viral vector

[00472] In some embodiments, polynucleotides of present invention may be packaged into oncolytic viruses, such as vaccine viruses. Oncolytic vaccine viruses may include viral particles of a thymidine kinase (TK)-deficient, granulocyte macrophage (GM)-colony stimulating factor (CSF)-expressing, replication-competent vaccinia virus vector sufficient to induce oncolysis of cells in the tumor (e.g., US Pat. NO.: 9,226,977).

5. Messenger RNA (mRNA)

[00473] In some embodiments, the effector modules of the invention may be designed as a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro, in vivo, in situ* or *ex vivo*. Such mRNA molecules may have the structural components or features of any of those taught in International Application number PCT/US2013/030062, the contents of which are incorporated herein by reference in its entirety.

[00474] Polynucleotides of the invention may also be designed as taught in, for example, Ribostem Limited in United Kingdom patent application serial number 0316089.2 filed on July 9, 2003 now abandoned, PCT application number PCT/GB2004/002981 filed on July 9, 2004 published as WO2005005622, United States patent application national phase entry serial number 10/563,897 filed on June 8, 2006 published as US20060247195 now abandoned, and European patent application national phase entry serial number EP2004743322 filed on July 9, 2004 published as EP1646714 now withdrawn; Novozymes, Inc. in PCT application number PCT/US2007/88060 filed on December 19, 2007 published as WO2008140615, United States patent application national phase entry serial number 12/520,072 filed on July 2, 2009 published

as US20100028943 and European patent application national phase entry serial number EP2007874376 filed on July 7, 2009 published as EP2104739; University of Rochester in PCT application number PCT/US2006/46120 filed on December 4, 2006 published as WO2007064952 and United States patent application serial number 11/606,995 filed on December 1, 2006 published as US20070141030; BioNTech AG in European patent application serial number EP2007024312 filed December 14, 2007 now abandoned, PCT application number PCT/EP2008/01059 filed on December 12, 2008 published as WO2009077134, European patent application national phase entry serial number EP2008861423 filed on June 2, 2010 published as EP2240572, United States patent application national phase entry serial number 12/,735,060 filed November 24, 2010 published as US20110065103, German patent application serial number DE 10 2005 046 490 filed September 28, 2005, PCT application PCT/EP2006/0448 filed September 28, 2006 published as WO2007036366, national phase European patent EP1934345 published March, 21, 2012 and national phase US patent application serial number 11/992,638 filed August 14, 2009 published as 20100129877; Immune Disease Institute Inc. in United States patent application serial number 13/088,009 filed April 15, 2011 published as US20120046346 and PCT application PCT/US2011/32679 filed April 15, 2011 published as WO20110130624; Shire Human Genetic Therapeutics in United States patent application serial number 12/957,340 filed on November 20, 2010 published as US20110244026; Sequitur Inc. in PCT application PCT/US1998/019492 filed on September 18, 1998 published as WO1999014346; The Scripps Research Institute in PCT application number PCT/US2010/00567 filed on February 24, 2010 published as WO2010098861, and United States patent application national phase entry serial number 13/203,229 filed November 3, 2011 published as US20120053333; Ludwig-Maximillians University in PCT application number PCT/EP2010/004681 filed on July 30, 2010 published as WO2011012316; Cellscript Inc. in United States patent number 8,039,214 filed June 30, 2008 and granted October 18, 2011, United States patent application serial numbers 12/962,498 filed on December 7, 2010 published as US20110143436, 12/962,468 filed on December 7, 2010 published as US20110143397, 13/237,451 filed on September 20, 2011 published as US20120009649, and PCT applications PCT/US2010/59305 filed December 7, 2010 published as WO2011071931 and PCT/US2010/59317 filed on December 7, 2010 published as WO2011071936; The Trustees of the University of Pennsylvania in PCT application number PCT/US2006/32372 filed on August 21, 2006 published as WO2007024708, and United States patent application national phase entry serial number 11/990,646 filed on March 27, 2009 published as US20090286852; Curevac GMBH in German patent application serial numbers DE10 2001 027 283.9 filed June 5, 2001, DE10 2001 062 480.8 filed December

19, 2001, and DE 20 2006 051 516 filed October 31, 2006 all abandoned, European patent numbers EP1392341 granted March 30, 2005 and EP1458410 granted January 2, 2008, PCT application numbers PCT/EP2002/06180 filed June 5, 2002 published as WO2002098443, PCT/EP2002/14577 filed on December 19, 2002 published as WO2003051401, PCT/EP2007/09469 filed on December 31, 2007 published as WO2008052770, PCT/EP2008/03033 filed on April 16, 2008 published as WO2009127230, PCT/EP2006/004784 filed on May 19, 2005 published as WO2006122828, PCT/EP2008/00081 filed on January 9, 2007 published as WO2008083949, and United States patent application serial numbers 10/729,830 filed on December 5, 2003 published as US20050032730, 10/870,110 filed on June 18, 2004 published as US20050059624, 11/914,945 filed on July 7, 2008 published as US20080267873, 12/446,912 filed on October 27, 2009 published as US2010047261 now abandoned, 12/522,214 filed on January 4, 2010 published as US20100189729, 12/787,566 filed on May 26, 2010 published as US20110077287, 12/787,755 filed on May 26, 2010 published as US20100239608, 13/185,119 filed on July 18, 2011 published as US20110269950, and 13/106,548 filed on May 12, 2011 published as US20110311472 all of which are herein incorporated by reference in their entirety.

[00475] In some embodiments, the effector modules may be designed as self-amplifying RNA. "Self-amplifying RNA" as used herein refers to RNA molecules that can replicate in the host resulting in the increase in the amount of the RNA and the protein encoded by the RNA. Such self-amplifying RNA may have structural features or components of any of those taught in International Patent Application Publication No. WO2011005799 (the contents of which are incorporated herein by reference in their entirety).

VI. DOSING, DELIVERY AND ADMINISTRATIONS

[00476] The compositions of the invention may be delivered to a cell or a subject through one or more routes and modalities. The viral vectors containing one or more effector modules, SREs, immunotherapeutic agents and other components described herein may be used to deliver them to a cell and/or a subject. Other modalities may also be used such as mRNAs, plasmids, and as recombinant proteins.

1. Delivery to cells

[00477] In another aspect of the invention, polynucleotides encoding biocircuits, effector modules, SREs (e.g., DDs), payloads of interest (immunotherapeutic agents) and compositions of the invention and vectors comprising said polynucleotides may be introduced into cells such as immune effector cells.

[00478] In one aspect of the invention, polynucleotides encoding biocircuits, effector modules, SREs (e.g., DDs), payloads of interest (immunotherapeutic agents) and compositions of the invention, may be packaged into viral vectors or integrated into viral genomes allowing transient or stable expression of the polynucleotides. Preferable viral vectors are retroviral vectors including lentiviral vectors. In order to construct a retroviral vector, a polynucleotide molecule encoding a biocircuit, an effector module, a DD or a payload of interest (i.e. an immunotherapeutic agent) is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. The recombinant viral vector is then introduced into a packaging cell line containing the gag, pol, and env genes, but without the LTR and packaging components. The recombinant retroviral particles are secreted into the culture media, then collected, optionally concentrated, and used for gene transfer. Lentiviral vectors are especially preferred as they are capable of infecting both dividing and non-dividing cells.

[00479] Vectors may also be transferred to cells by non-viral methods by physical methods such as needles, electroporation, sonoporation, hyrdoporation; chemical carriers such as inorganic particles (e.g. calcium phosphate, silica, gold) and/or chemical methods. In some embodiments, synthetic or natural biodegradable agents may be used for delivery such as cationic lipids, lipid nano emulsions, nanoparticles, peptide based vectors, or polymer based vectors.

[00480] In some embodiments, the polypeptides of the invention may be delivered to the cell directly. In one embodiment, the polypeptides of the invention may be delivered using synthetic peptides comprising an endosomal leakage domain (ELD) fused to a cell penetration domain (CLD). The polypeptides of the invention are co introduced into the cell with the ELD-CLD-synthetic peptide. ELDs facilitate the escape of proteins that are trapped in the endosome, into the cytosol. Such domains are derived proteins of microbial and viral origin and have been described in the art. CPDs allow the transport of proteins across the plasma membrane and have also been described in the art. The ELD-CLD fusion proteins synergistically increase the transduction efficiency when compared to the co-transduction with either domain alone. In some embodiments, a histidine rich domain may optionally be added to the shuttle construct as an additional method of allowing the escape of the cargo from the endosome into the cytosol. The shuttle may also include a cysteine residue at the N or C terminus to generate multimers of the fusion peptide. Multimers of the ELD-CLD fusion peptides generated by the addition of cysteine residue to the terminus of the peptide show even greater transduction efficiency when compared to the single fusion peptide constructs. The polypeptides of the invention may also be appended to appropriate localization signals to direct the cargo to the appropriate sub-cellular location e.g. nucleus. In some embodiments any of the ELDs, CLDs or the fusion ELD-CLD

synthetic peptides taught in the International Patent Publication, WO2016161516 and WO2017175072 may be useful in the present invention (the contents of each of which are herein incorporated by reference in their entirety).

2. Dosing

[00481] The present invention provides methods comprising administering any one or more compositions for immunotherapy to a subject in need thereof. These may be administered to a subject using any amount and any route of administration effective for preventing or treating a clinical condition such as cancer, infection diseases and other immunodeficient diseases.

[00482] Compositions in accordance with the invention are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, or prophylactically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, previous or concurrent therapeutic interventions and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[00483] Compositions of the invention may be used in varying doses to avoid T cell energy, prevent cytokine release syndrome and minimize toxicity associated with immunotherapy. For example, low doses of the compositions of the present invention may be used to initially treat patients with high tumor burden, while patients with low tumor burden may be treated with high and repeated doses of the compositions of the invention to ensure recognition of a minimal tumor antigen load. In another instance, the compositions of the present invention may be delivered in a pulsatile fashion to reduce tonic T cell signaling and enhance persistence *in vivo*. In some aspects, toxicity may be minimized by initially using low doses of the compositions of the invention, prior to administering high doses. Dosing may be modified if serum markers such as ferritin, serum C-reactive protein, IL6, IFN-γ, and TNF-α are elevated.

[00484] In some embodiments, the neurotoxicity may be associated with CAR or TIL therapy. Such neurotoxicity may be associated CD19-CARs. Toxicity may be due to excessive T cell infiltration into the brain. In some embodiments, neurotoxicity may be alleviated by preventing the passage of T cells through the blood brain barrier. This can be achieved by the targeted gene

deletion of the endogenous alpha-4 integrin inhibitors such as tysabri/natalizumab may also be useful in the present invention.

3. Administration

[00485] In some embodiments, the compositions for immunotherapy may be administered to cells *ex vivo* and subsequently administered to the subject. Immune cells can be isolated and expanded *ex vivo* using a variety of methods known in the art. For example, methods of isolating cytotoxic T cells are described in U.S. Pat. NOs. 6,805,861 and 6,531, 451; the contents of each of which are incorporated herein by reference in their entirety. Isolation of NK cells is described in U.S. Pat. NOs.: 7,435, 596; the contents of which are incorporated by reference herein in its entirety.

[00486] In some embodiments, compositions of the present invention, may be administered by any of the methods of administration taught in the copending commonly owned U.S. Provisional Patent Application No. 62/320,864 filed on 4/11/2016, or in US Provisional Application No. 62/466,596 filed March 3, 2017 and the International Publication WO2017/180587, the contents of each of which are incorporated herein by reference in their entirety.

[00487] In some embodiments, depending upon the nature of the cells, the cells may be introduced into a host organism e.g. a mammal, in a wide variety of ways including by injection, transfusion, infusion, local instillation or implantation. In some aspects, the cells of the invention may be introduced at the site of the tumor. The number of cells that are employed will depend upon a number of circumstances, the purpose for the introduction, the lifetime of the cells, the protocol to be used, for example, the number of administrations, the ability of the cells to multiply, or the like. The cells may be in a physiologically-acceptable medium.

[00488] In some embodiments, the cells of the invention may be administrated in multiple doses to subjects having a disease or condition. The administrations generally effect an improvement in one or more symptoms of cancer or a clinical condition and/or treat or prevent cancer or clinical condition or symptom thereof.

[00489] In some embodiments, the compositions for immunotherapy may be administered *in vivo*. In some embodiments, polypeptides of the present invention comprising biocircuits, effector molecules, SREs, payloads of interest (immunotherapeutic agents) and compositions of the invention may be delivered in vivo to the subject. In vivo delivery of immunotherapeutic agents is well described in the art. For example, methods of delivery of cytokines are described in the E.P. Pat. No.: EP0930892 A1, the contents of which are incorporated herein by reference.

[00490] In one embodiment, the payloads of the present invention may be administered in conjunction with inhibitors of SHP-1 and/or SHP-2. The tyrosine-protein phosphatase SHP1

(also known as PTPN6) and SHP2 (also known as PTPN11) are involved in the Programmed Cell Death (PD1) inhibitory signaling pathway. The intracellular domain of PD1 contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). ITSM has been shown to recruit SHP-1 and 2. This generates negative costimulatory micro clusters that induce the dephosphorylation of the proximal TCR signaling molecules, thereby resulting in suppression of T cell activation, which can lead to T cell exhaustion. In one embodiment, inhibitors of SHP-1 and 2 may include expressing dominant negative versions of the proteins in T cells, TILs or other cell types to relieve exhaustion. Such mutants can bind to the endogenous, catalytically active proteins, and inhibit their function. In one embodiment, the dominant negative mutant of SHP-1 and/ or SHP-2 lack the phosphatase domain required for catalytic activity. In some embodiments, any of the dominant negative SHP-1 mutants taught Bergeron S et al. (2011). Endocrinology. 2011 Dec;152(12):4581-8.; Dustin JB et al. (1999) J Immunol. Mar 1;162(5):2717-24.; Berchtold S (1998) Mol Endocrinol. Apr;12(4):556-67 and Schram et al. (2012) Am J Physiol Heart Circ Physiol. 1;302(1):H231-43.; may be useful in the invention (the contents of each of which are incorporated by reference in their entirety).

Routes of delivery

[00491] The pharmaceutical compositions, biocircuits, biocircuit components, effector modules including their SREs (e.g., DDs), payloads (i.e. immunotherapeutic agents), vectors and cells of the present invention may be administered by any route to achieve a therapeutically effective outcome.

[00492] These include, but are not limited to enteral (into the intestine), gastroenteral, epidural (into the dura matter), oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracranial (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intrasinal infusion, intravitreal, (through the eye), intravenous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival,

cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), intramyocardial (entering the myocardium), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal.

VII. DEFINITIONS

[00493] At various places in the present specification, features or functions of the compositions of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub combination of the members of such groups and ranges. The following is a non-limiting list of term definitions.

[00494] *Activity*: As used herein, the term "activity" refers to the condition in which things are happening or being done. Compositions of the invention may have activity and this activity may involve one or more biological events. In some embodiments, biological events may include cell signaling events. In some embodiments, biological events may include cell signaling events associated protein interactions with one or more corresponding proteins, receptors, small molecules or any of the biocircuit components described herein.

[00495] *Adoptive cell therapy (ACT)*: The terms "Adoptive cell therapy" or "Adoptive cell transfer", as used herein, refer to a cell therapy involving in the transfer of cells into a patient, wherein cells may have originated from the patient, or from another individual, and are engineered (altered) before being transferred back into the patient. The therapeutic cells may be derived from the immune system, such as Immune effector cells: CD4+ T cell; CD8+ T cell, Natural Killer cell (NK cell); and B cells and tumor infiltrating lymphocytes (TILs) derived from the resected tumors. Most commonly transferred cells are autologous anti-tumor T cells after *ex vivo* expansion or manipulation. For example, autologous peripheral blood lymphocytes can be genetically engineered to recognize specific tumor antigens by expressing T-cell receptors (TCR) or chimeric antigen receptor (CAR).

[00496] *Agent*: As used herein, the term "agent" refers to a biological, pharmaceutical, or chemical compound. Non-limiting examples include simple or complex organic or inorganic molecule, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, antibody fragment, a receptor, and soluble factor.

[00497] *Agonist*: the term "agonist" as used herein, refers to a compound that, in combination with a receptor, can produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, for example, (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise resulting in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular receptor or family of receptors, e.g., agonist of a co-stimulatory receptor.

[00498] *Antagonist*: the term "antagonist" as used herein refers to any agent that inhibits or reduces the biological activity of the target(s) it binds.

[00499] *Antigen*: the term "antigen" as used herein is defined as a molecule that provokes an immune response when it is introduced into a subject or produced by a subject such as tumor antigens which arise by the cancer development itself. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells such as cytotoxic T lymphocytes and T helper cells, or both. An antigen can be derived from organisms, subunits of proteins/antigens, killed or inactivated whole cells or lysates. In the context of the invention, the terms "antigens of interest" or "desired antigens" refers to those proteins and/or other biomolecules provided herein that are immunospecifically bound or interact with antibodies of the present invention and/or fragments, mutants, variants, and/or alterations thereof described herein. In some embodiments, antigens of interest may comprise any of the polypeptides or payloads or proteins described herein, or fragments or portions thereof.

[00500] *Approximately*: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100 of a possible value).

[00501] *Associated with*: As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, mean that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serve as linking agents, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, e.g., physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[00502] *Autologous*: the term "autologous" as used herein is meant to refer to any material derived from the same individual to which it is later to be re-introduced into the individual.

[00503] *Barcode*: the term "barcode" as used herein refers to polynucleotide or amino acid sequence that distinguishes one polynucleotide or amino acid from another.

[00504] *Cancer*: the term "cancer" as used herein refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues ultimately metastasize to distant parts of the body through the lymphatic system or bloodstream.

[00505] *Co-stimulatory molecule*: As used herein, in accordance with its meaning in immune T cell activation, refers to a group of immune cell surface receptor/ligands which engage between T cells and APCs and generate a stimulatory signal in T cells which combines with the stimulatory signal in T cells that results from T cell receptor (TCR) recognition of antigen/MHC complex (pMHC) on APCs

[00506] *Cytokines*: the term "cytokines", as used herein, refers to a family of small soluble factors with pleiotropic functions that are produced by many cell types that can influence and regulate the function of the immune system.

[00507] *Delivery*: the term "delivery" as used herein refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload. A "delivery agent" refers to any agent which facilitates, at least in part, the in vivo delivery of one or more substances (including, but not limited to a compound and/or compositions of the present invention) to a cell, subject or other biological system cells.

[00508] *Destabilized*: As used herein, the term "destable," "destabilize," "destabilizing region" or "destabilizing domain" means a region or molecule that is less stable than a starting, reference, wild-type or native form of the same region or molecule.

[00509] *Engineered*: As used herein, embodiments of the invention are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[00510] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; (4) folding of a polypeptide or protein; and (5) post-translational modification of a polypeptide or protein.

[00511] *Feature*: As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[00512] *Formulation*: As used herein, a "formulation" includes at least a compound and/or composition of the present invention and a delivery agent.

[00513] *Fragment*: A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein. In some embodiments, a fragment of a protein includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250 or more amino acids. In some embodiments, fragments of an antibody include portions of an antibody.

[00514] *Functional*: As used herein, a "functional" biological molecule is a biological entity with a structure and in a form in which it exhibits a property and/or activity by which it is characterized.

[00515] *Immune cells*: the term "an immune cell", as used herein, refers to any cell of the immune system that originates from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid progenitor cell (which give rise to myeloid cells such as monocytes, macrophages, dendritic cells, megakaryocytes and granulocytes) and a lymphoid progenitor cell (which give rise to lymphoid cells such as T cells, B cells and natural killer (NK) cells). Exemplary immune system cells include a CD4+ T cell, a CD8+ T cell, a CD4− CD8− double negative T cell, a T γδ cell, a Tαβ cell, a regulatory T cell, a natural killer cell, and a dendritic cell. Macrophages and dendritic cells may be referred to as "antigen presenting cells" or "APCs," which are specialized cells that can activate T cells when a major histocompatibility complex (MHC) receptor on the surface of the APC complexed with a peptide interacts with a TCR on the surface of a T cell.

[00516] *Immunotherapy*: the term "immunotherapy" as used herein, refers to a type of treatment of a disease by the induction or restoration of the reactivity of the immune system towards the disease.

[00517] *Immunotherapeutic agent:* the term "immunotherapeutic agent" as used herein, refers to the treatment of disease by the induction or restoration of the reactivity of the immune system towards the disease with a biological, pharmaceutical, or chemical compound.

[00518] *In vitro:* As used herein, the term "in vitro" refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, in a Petri dish, etc., rather than within an organism (e.g., animal, plant, or microbe).

[00519] *In vivo*: As used herein, the term "in vivo" refers to events that occur within an organism (e.g., animal, plant, or microbe or cell or tissue thereof).

[00520] *Linker*: As used herein, a linker refers to a moiety that connects two or more domains, moieties or entities. In one embodiment, a linker may comprise 10 or more atoms. In a further embodiment, a linker may comprise a group of atoms, e.g., 10-1,000 atoms, and can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. In some embodiments, a linker may comprise one or more nucleic acids comprising one or more nucleotides. In some embodiments, the linker may comprise an amino acid, peptide, polypeptide or protein. In some embodiments, a moiety bound by a linker may include, but is not limited to an atom, a chemical group, a nucleoside, a nucleotide, a nucleobase, a sugar, a nucleic acid, an amino acid, a peptide, a polypeptide, a

protein, a protein complex, a payload (e.g., a therapeutic agent). or a marker (including, but not limited to a chemical, fluorescent, radioactive or bioluminescent marker). The linker can be used for any useful purpose, such as to form multimers or conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl, amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (e.g., ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers, Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bonds include an amido bond which may be cleaved for example by the use of tris(2-carboxyethyl) phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond which may be cleaved for example by acidic or basic hydrolysis.

[00521] *Checkpoint/factor*: As used herein, a checkpoint factor is any moiety or molecule whose function acts at the junction of a process. For example, a checkpoint protein, ligand or receptor may function to stall or accelerate the cell cycle.

[00522] *Metabolite:* Metabolites are the intermediate products of metabolic reactions catalyzed by enzymes that naturally occur within cells. This term is usually used to describe small molecules, fragments of larger biomolecules or processed products.

[00523] *Modified*: As used herein, the term "modified" refers to a changed state or structure of a molecule or entity as compared with a parent or reference molecule or entity. Molecules may be modified in many ways including chemically, structurally, and functionally. In some embodiments, compounds and/or compositions of the present invention are modified by the introduction of non-natural amino acids.

[00524] *Mutation*: As used herein, the term "mutation" refers to a change and/or alteration. In some embodiments, mutations may be changes and/or alterations to proteins (including peptides and polypeptides) and/or nucleic acids (including polynucleic acids). In some embodiments, mutations comprise changes and/or alterations to a protein and/or nucleic acid sequence. Such changes and/or alterations may comprise the addition, substitution and or deletion of one or more amino acids (in the case of proteins and/or peptides) and/or nucleotides (in the case of nucleic acids and or polynucleic acids e.g., polynucleotides). In some embodiments, wherein mutations comprise the addition and/or substitution of amino acids and/or nucleotides, such additions

and/or substitutions may comprise 1 or more amino acid and/or nucleotide residues and may include modified amino acids and/or nucleotides. The resulting construct, molecule or sequence of a mutation, change or alteration may be referred to herein as a mutant.

[00525] *Neoantigen*: the term "neoantigen", as used herein, refers to a tumor antigen that is present in tumor cells but not normal cells and do not induce deletion of their cognate antigen specific T cells in thymus (i.e., central tolerance). These tumor neoantigens may provide a "foreign" signal, similar to pathogens, to induce an effective immune response needed for cancer immunotherapy. A neoantigen may be restricted to a specific tumor. A neoantigen be a peptide/protein with a missense mutation (missense neoantigen), or a new peptide with long, completely novel stretches of amino acids from novel open reading frames (neoORFs). The neoORFs can be generated in some tumors by out-of-frame insertions or deletions (due to defects in DNA mismatch repair causing microsatellite instability), gene-fusion, read-through mutations in stop codons, or translation of improperly spliced RNA (e.g., Saeterdal et al., *Proc Natl Acad Sci USA*, 2001, 98: 13255-13260).

[00526] *Off-target*: As used herein, "off target" refers to any unintended effect on any one or more target, gene, cellular transcript, cell, and/or tissue.

[00527] *Operably linked*: As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[00528] *Payload or payload of interest (POI)*: the terms "payload" and "payload of interest (POI)", as used herein, are used interchangeable. A payload of interest (POI) refers to any protein or compound whose function is to be altered. In the context of the present invention, the POI is a component in the immune system, including both innate and adaptive immune systems. Payloads of interest may be a protein, a fusion construct encoding a fusion protein, or non-coding gene, or variant and fragment thereof. Payload of interest may, when amino acid based, may be referred to as a protein of interest.

[00529] *Pharmaceutically acceptable excipients*: the term "pharmaceutically acceptable excipient," as used herein, refers to any ingredient other than active agents (e.g., as described herein) present in pharmaceutical compositions and having the properties of being substantially nontoxic and non-inflammatory in subjects. In some embodiments, pharmaceutically acceptable excipients are vehicles capable of suspending and/or dissolving active agents. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients

include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[00530] *Pharmaceutically acceptable salts*: Pharmaceutically acceptable salts of the compounds described herein are forms of the disclosed compounds wherein the acid or base moiety is in its salt form (e.g., as generated by reacting a free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Pharmaceutically acceptable salts include the conventional non-toxic salts, for example, from non-toxic inorganic or organic acids. In some embodiments, a pharmaceutically acceptable salt is prepared from a parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, Pharmaceutical Salts: Properties,

Selection, and Use, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., Journal of Pharmaceutical Science, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety. Pharmaceutically acceptable solvate: The term "pharmaceutically acceptable solvate," as used herein, refers to a crystalline form of a compound wherein molecules of a suitable solvent are incorporated in the crystal lattice. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), N-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), N, N'-dimethylformamide (DMF), N, N'-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate." In some embodiments, the solvent incorporated into a solvate is of a type or at a level that is physiologically tolerable to an organism to which the solvate is administered (e.g., in a unit dosage form of a pharmaceutical composition).

[00531] *Stable*: As used herein "stable" refers to a compound or entity that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[00532] *Stabilized*: As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable. In some embodiments, stability is measured relative to an absolute value. In some embodiments, stability is measured relative to a secondary status or state or to a reference compound or entity.

[00533] *Standard CAR*: As used herein, the term "standard CAR" refers to the standard design of a chimeric antigen receptor. The components of a CAR fusion protein including the extracellular scFv fragment, transmembrane domain and one or more intracellular domains are linearly constructed as a single fusion protein.

[00534] *Stimulus response element (SRE)*: the term "stimulus response element (SRE), as used herein, is a component of an effector module which is joined, attached, linked to or associated with one or more payloads of the effector module and in some instances, is responsible for the responsive nature of the effector module to one or more stimuli. As used herein, the "responsive" nature of an SRE to a stimulus may be characterized by a covalent or non-covalent interaction, a direct or indirect association or a structural or chemical reaction to the stimulus. Further, the response of any SRE to a stimulus may be a matter of degree or kind. The response may be a partial response. The response may be a reversible response. The response may ultimately lead to

a regulated signal or output. Such output signal may be of a relative nature to the stimulus, e.g., producing a modulatory effect of between 1 and 100 or a factored increase or decrease such as 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more. One non-limiting example of an SRE is a destabilizing domain (DD).

[00535] *Subject*: As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[00536] *T cell*: A T cell is an immune cell that produces T cell receptors (TCRs). T cells can be naïve (not exposed to antigen; increased expression of CD62L, CCR7, CD28, CD3, CD127, and CD45RA, and decreased expression of CD45RO as compared to T_{CM}), memory T cells (T_M) (antigen-experienced and long-lived), and effector cells (antigen-experienced, cytotoxic). T_M can be further divided into subsets of central memory T cells (T_{CM}, increased expression of CD62L, CCR7, CD28, CD127, CD45RO, and CD95, and decreased expression of CD54RA as compared to naïve T cell and effector memory T cells (T_{EM}, decreased expression of CD62L, CCR7, CD28, CD45RA, and increased expression of CD127 as compared to naïve T cells or T_{CM}). Effector T cells (T_E) refers to antigen-experienced CD8+ cytotoxic T lymphocytes that have decreased expression of CD62L, CCR7, CD28, and are positive for granzyme and perforin as compared to T_{CM}. Other exemplary T cells include regulatory T cells, such as CD4+ CD25+ (Foxp3+) regulatory T cells and Treg17 cells, as well as Tr1, Th3, CD8+CD28−, and Qa-1 restricted T cells.

[00537] *T cell receptor*: T cell receptor (TCR) refers to an immunoglobulin superfamily member having a variable antigen binding domain, a constant domain, a transmembrane region, and a short cytoplasmic tail, which is capable of specifically binding to an antigen peptide bound to a MHC receptor. A TCR can be found on the surface of a cell or in soluble form and generally is comprised of a heterodimer having α and β chains (also known as TCRα and TCRβ, respectively), or γ and δ chains (also known as TCRγ and TCRδ, respectively). The extracellular portion of TCR chains (e.g., α-chain, β-chain) contains two immunoglobulin domains, a variable domain (e.g., α-chain variable domain or V_α, β-chain variable domain or V_β) at the N-terminus, and one constant domain (e.g., α-chain constant domain or C_α and β-chain constant domain or C_β,) adjacent to the cell membrane. Similar to immunoglobulin, the variable domains contain complementary determining regions (CDRs) separated by framework regions (FRs). A TCR is usually associated with the CD3 complex to form a TCR complex. As used herein, the term "TCR complex" refers to a complex formed by the association of CD3 with TCR. For example, a

TCR complex can be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRα chain, and a TCRβ chain. Alternatively, a TCR complex can be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRγ chain, and a TCRδ chain. A "component of a TCR complex," as used herein, refers to a TCR chain (i.e., TCRα, TCRβ, TCRγ or TCRδ), a CD3 chain (i.e., CD3γ, CD3δ, CD3ε or CD3ζ), or a complex formed by two or more TCR chains or CD3 chains (e.g., a complex of TCRα and TCRβ, a complex of TCRγ and TCRδ, a complex of CD3ε and CD3δ, a complex of CD3γ and CD3ε, or a sub-TCR complex of TCRα, TCRβ, CD3γ, CD3δ, and two CD3ε chains.

[00538] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (e.g., nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, etc.) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen comprising a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to comprise a therapeutically effective amount of a particular agent or entity if it comprises an amount that is effective when administered as part of such a dosage regimen.

[00539] *Treatment or treating:* As used herein, the terms "treatment" or "treating" denote an approach for obtaining a beneficial or desired result including and preferably a beneficial or desired clinical result. Such beneficial or desired clinical results include, but are not limited to, one or more of the following: reducing the proliferation of (or destroying) cancerous cells or other diseased, reducing metastasis of cancerous cells found in cancers, shrinking the size of the tumor, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of individuals.

[00540] *Tune:* As used herein, the term "tune" means to adjust, balance or adapt one thing in response to a stimulus or toward a particular outcome. In one non-limiting example, the SREs and/or DDs of the present invention adjust, balance or adapt the function or structure of compositions to which they are appended, attached or associated with in response to particular stimuli and/or environments.

EQUIVALENTS AND SCOPE

[00541] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00542] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in or otherwise relevant to a given product or process.

[00543] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[00544] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00545] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00546] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

EXAMPLES

Example 1. Generation of novel ligand responsive SREs or DDs by mutagenesis screening

Study design

[00547] To engineer constructs that display ligand dependent stability, a candidate ligand binding domain (LBD) is selected and a cell-based screen using yellow fluorescent protein (YFP) as a reporter for protein stability is designed to identify mutants of the candidate LBD possessing the desired characteristics of a destabilizing domain: low protein levels in the absence of a ligand of the LBD, (i.e., low basal stability), large dynamic range, robust and predictable dose-response behavior, and rapid kinetics of degradation (Banaszynski, *et al.*, (2006) *Cell*; 126(5): 995–1004). The candidate LBD binds to a desired ligand but not endogenous signaling molecules.

[00548] The candidate LBD sequence (as a template) is first mutated using a combination of nucleotide analog mutagenesis and error-prone PCR, to generate libraries of mutants based on the template candidate domain sequence. The libraries generated are cloned in-frame at either the 5′- or 3′-ends of the YFP gene, and a retroviral expression system is used to stably transduce the libraries of YFP fusions into NIH3T3 fibroblasts.

[00549] The transduced NIH3T3 cells are subjected to three to four rounds of sorting using fluorescence-activated cell sorting (FACS) to screen the libraries of candidate DDs. Transduced NIH3T3 cells are cultured in the absence of the high affinity ligand of the ligand binding domain (LBD), and cells that exhibit low levels of YFP expression are selected through FACS.

Screening Strategy I

[00550] The selected cell population is cultured in the presence of the high affinity ligand of the ligand binding domain for a period of time (e.g., 24 hours), at which point cells are sorted again by FACS. Cells that exhibit high levels of YFP expression are selected through FACS and the selected cell population is split into two groups and treated again with the high affinity ligand of the ligand binding domain at different concentrations; one group is treated with the lower concentration of the ligand and the other is treated with a high concentration of the ligand, for a period of time (e.g., 24 hours), at which point cells are sorted again by FACS. Cells expressing mutants that are responsive to lower concentrations of the ligand are isolated.

[00551] The isolated cells responsive to the lower concentration of the ligand are treated with the ligand again and cells exhibiting low fluorescence levels are collected 4 hours following removal of the ligand from the media. This fourth sorting is designed to enrich cells that exhibit fast kinetics of degradation (Iwamoto *et al.*, *Chem Biol.* 2010 Sep 24; 17(9): 981–988).

Screening Strategy II

[00552] The selected cell population is subject to additional one or more sorts by FACS in the absence of high affinity ligand of LBD and cells that exhibit low levels of YFP expression are selected for further analysis. Cells are treated with high affinity ligand of the ligand binding domain, for a period of time (e.g. 24 hours), and sorted again by FACS. Cells expressing high levels of YFP are selected for through FACS. Cells with high expression of YFP are treated with ligand again and cells exhibiting low fluorescence levels are collected 4 hours following removal of the ligand from the media to enrich cells that exhibit fast kinetics of degradation. Any of the sorting steps may be repeated to identify DDs with ligand dependent stability.

[00553] The cells are recovered after sorting. The identified candidate cells are harvested and the genomic DNA is extracted. The candidate DDs are amplified by PCR and isolated. The candidate DDs are sequenced and compared to the LBD template to identify the mutations in candidate DDs.

Example 2. DD regulated recombinant IL12 expression

[00554] FKBP (DD)-IL12 and DHFR (DD)-IL12 constructs were packaged into pLVX IRES-Puro lentiviral vectors with CMV, EF1a, or PGK promoters or without a promoter. The IL12 consists of two subunits, p40 and p35 which are separated by a linker. A p40 signal sequence was inserted next to the DD or IL12. In several constructs, a furin protease cleavage site or a modified furin site was included.

[00555] HEK293T cells were transiently transfected with 200ng or 1μg of FKBP-IL12 plasmids (OT-IL12-001 to OT-IL12-005), and subsequently treated with 10μM Shield-1 or vehicle control for 6 hours. Culture media was collected from transfected cells and diluted 1:50 to measure IL12 levels using p40 ELISA. The stabilization ratio was defined as fold change in IL12 expression with ligand treatment compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired. The average IL12 ELISA readings and stabilization ratio are presented in Table 15.

Table 15: Ligand dependent IL12 induction

Construct ID	Vehicle	10μM Shield-1	Stabilization ratio
OT-IL12-001	1289.61	1748.95	1.36
OT-IL12-002	18.01	50.73	2.82
OT-IL12-003	1762.55	2138.25	1.21
OT-IL12-004	385.95	1567.62	4.06
OT-IL12-005	1188.42	2670.80	2.25
HEK293T	-12.921	-22.015	

[00556] OT-IL12-002 and OT- IL12-004 showed low level of IL12 expression in the absence of ligand when compared to IL12 levels in HEK 293T parental cells. Treatment with Shield-1 resulted in an increase in IL12 levels in OT-IL12-002, OT-IL12-004, and OT-IL12-005 constructs and a stabilization ratio between 2 and 4. These data show that OT-IL12-002 and OT-IL12-004 are destabilized in the absence of these constructs are stabilized by Shield-1.

[00557] IL12 expression was measured in cells following stable transduction. 500,000 cells stably transduced with OT-IL12-004 were plated in a 12 well plate and incubated overnight in growth media consisting of Dulbecco's Modified Eagle medium (DMEM) and 10% fetal bovine serum (FBS). The next day, cells were treated with 1μM Shield-1 or vehicle control for 6 or 24 hours. Following treatment with Shield-1, growth media was collected from the cells and diluted 10, 40, 160 or 640 fold and IL12 levels were quantified using IL12-p40 ELISA. The stabilization ratio was defined as fold change in IL12 expression with ligand treatment compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired. The average IL12 ELISA readings and stabilization ratio at 6 hours are presented in Table 16.

Table 16: Ligand dependent IL12 induction (6 hours)

Media dilution (fold)	6 hours		
	Vehicle	Shield-1	Stabilization ratio
10	0.17	0.58	3.35
40	0.10	0.26	2.62
160	0.08	0.12	1.41
640	0.09	0.08	0.93

[00558] IL12 stabilization ratio greater than 1 was observed at 10, 40 and 160-fold dilutions of media, indicating that IL12 is stabilized by Shield-1 treatment at these dilutions at 6 hours.

[00559] The average IL12 ELISA readings and stabilization ratio at 24 hours are presented in Table 17.

Table 17: Ligand dependent IL12 induction (24 hours)

Media dilution (fold)	24 hours		
	Vehicle	Shield-1	Stabilization ratio
10	0.28	1.33	4.69
40	0.12	0.79	6.39
160	0.09	0.30	3.44
640	0.08	0.12	1.46

[00560] IL12 stabilization ratio was greater than 1 at all media dilutions tested and the highest stabilization ratio was observed at 40-fold dilution of media at 24 hours, suggesting ligand dependent stabilization.

[00561] To evaluate Shield-1 dependent FKBP-1L12 induction over time, 2 million cells were plated in growth medium and incubated overnight in the presence of 1μM Shield-1 or vehicle control. Cells were then incubated for with the ligand for 2, 4,6, 8, 24, 48, or 72 hours and growth media was collected for the cells at all time points. Growth media was diluted 400-fold and IL12 levels were measured using IL12 p40 ELISA. The stabilization ratio was defined as fold change in IL12 expression with ligand treatment compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired. Average IL12 ELISA readings and stabilization ratio are presented in Table 18.

Table 18: IL12 induction over time

Time (hrs)	Vehicle	Shield-1	Stabilization ratio
2	0.13	0.18	1.41
4	0.14	0.26	1.89
6	0.13	0.29	2.30
8	0.14	0.28	1.99
24	0.18	0.99	5.47
48	0.23	1.79	7.71
72	0.26	1.63	6.28

[00562] Stabilization ratio increased over time and peaked at 48 hours, suggesting that IL12 is stabilized by Shield-1 with increasing duration of ligand treatment.

[00563] To evaluate the dependence of FKBP-IL12 production on Shield-1 dose levels, OT-IL12-004 transduced HEK293T cells were plated at different densities (40,000 cells, 20,000 cells, 10,000 cells or 5,000 cells per well) onto a 96-well plate. Following overnight incubation, cells were treated with growth medium containing 0 to 10μM Shield-1 for 24 hours. Media was then collected, diluted 400-fold and FKBP-IL12 levels were measured using IL12-p40 ELISA. Average IL12 ELISA readings are presented in Table 19.

Table 19: Dose and cell number dependent IL12 induction

Shield-1 (μM)	40000 cells/well	20000 cells/well	10000 cells/well	5000 cells/well
10	623.77	656.70	214.11	193.62
3.333333	670.64	618.10	273.74	207.55
1.111111	677.27	872.24	322.56	203.71
0.37037	368.17	582.71	250.49	172.50
0.123457	197.29	343.34	156.98	95.92
0.041152	171.50	205.68	63.79	48.89
0.013717	117.25	103.56	13.30	-2.35
0.004572	66.34	60.58	2.11	-8.53
0.001524	100.43	39.55	-13.58	-21.76

0	83.49	7.92	-21.76	-26.97

[00564] A dose dependent IL12 induction was observed at all cell numbers tested. IL12 induction increased with Shield-1 up to a dose of 1μM; following which IL12 induction plateaued. Notably, greater IL12 induction was observed at 2000 and 4000 cells/well.

Example 3. DD regulated recombinant IL12 mediated functions in HEK293T cells

[00565] HEK-Blue sensor cells (InvivoGen, San Diego, CA) were utilized to evaluate whether DD regulated IL12 is capable of regulating signaling downstream of IL12. In these cells, the IL12 receptor, STAT4 and downstream transcriptional elements are linked to a reporter gene such that IL12 signaling can be monitored. One million HEK 293T were transfected with 200ng of OT-IL12-003 plasmid using Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA). 48 hours after transfection, cells were treated with growth media containing 10μM Shield-1, incubated for another 24 hours, following which, media was collected. 50,000 HEK 293 Blue sensor cells were plated onto 96 well plates and incubated overnight with media (at different dilutions) from Shield-1 treated OT-IL12-003 expressing HEK293T cells. After overnight incubation, 20 μl media was removed from each well and incubated with 180 μl Quanti-Blue reagent (InvivoGen, San Diego, CA) for 30 minutes at 37°C. Absorption was measured at 620 nm using a spectrophotometer. To generate a standard curve, 180 μl Quanti-Blue reagent was mixed with 20 μl of recombinant IL12 at following concentrations 500, 250, 125, 62.5, 31.25, 15.62, 7.8 and 3.9 pg/ml. Functional IL12 concentrations were determined by comparing the optical density of each sample with IL12 standard curve. Measurable levels of functional IL12 were reached with 640-fold dilutions of IL12 containing growth media and further plateaued at higher concentrations of the media (Figure 19A).

[00566] The dependence of functional IL12 production on the dose of Shield-1 used was measured. 10,000 HEK293T cells stably transduced with OT-IL12-004 were plated onto 96 well plates and treated with growth media containing 10, 3.33, 1.11, 0.37, 0.12, 0.04, 0.01, 0.005, 0.002 or 0 μM Shield-1 for 24 hours. Following Shield-1 treatment, media from cells was diluted 200-fold and 20μL of the diluted media was added to HEK Blue sensor cells. After overnight incubation, 20 μl of media was removed from each well and incubated with 180 μl Quanti-Blue reagent (InvivoGen, San Diego, CA) for 30 minutes at 37°C. Absorption was measured at 620 nm using a spectrophotometer. To generate a standard curve, 180 μl Quanti-Blue reagent was mixed with 20 μl of recombinant IL12 at following concentrations 500, 250, 125, 62.5, 31.25, 15.62, 7.8 and 3.9 pg/ml. Functional IL12 concentrations were determined by comparing the

optical density of each sample with IL12 standard curve. A dose dependent increase in the levels of functional IL12 levels was observed (Figure 19B).

Example 4. DD regulated recombinant IL12 expression *in vivo*

[00567] SKOV3 tumor cells expressing FBP regulated-IL12 (#OT-IL12-009) or parental cells were implanted into SCID Beige mice (Day 0). Mice implanted with FKBP IL12 were dosed intraperitoneally with Shield-1 (10mg/kg) or vehicle control on Day 2 and Day 7, while the parental cells were left untreated. Blood samples were collected at 0, 2, 4, 6, 8 and 24 hours after Shield-1 dosing and plasma human IL12 levels were measured using ELISA. The average adjusted concentration of plasma IL12 is presented in Figure 19C. At Day 2, IL12 levels increased in Shield-1 treatment and the levels were higher than vehicle control at 4, 6, 8, and 24 hours. Maximum IL12 levels were detected in Shield-1 treated mice at 8 hours following treatment. In contrast, at day 7, IL12 levels were very low and almost comparable to the IL12 levels in parental SKOV3 cells.

[00568] The experiment was repeated 28 days following implantation of SKOV3 tumor cells. Mice were split into three groups, with the groups receiving 1, 2 or 3 doses of ligand or vehicle control. Mice received multiple doses with a two-hour interval. Blood samples were collected right before the first dose (0 hours), and 6 hours and 24 hours after the first dosing. Plasma IL12 levels were measured and average IL12 concentrations are shown in Figure 19D. The two dose and three dosing scheme resulted in higher plasma IL12 levels when compared to vehicle treated samples. Peak plasma IL12 levels was detected at 6 hours following shield-1 treatment with all dosing schemes, and the highest IL12 plasma levels were detected with the three-dose regimen. This demonstrates the ligand dependent stabilization of IL12 *in vivo*.

Example 5. DD regulated IL15

[00569] To test ligand dependent IL15 production, 1 million HEK-293T cells were plated in a 6-well plate in growth media containing DMEM and 10% FBS and incubated overnight at 37°C at 5% CO2. Cells were then transfected with 100ng of OT-IL15-001(constitutive) or OT-IL15-002 (ecDHFR-IL15) using Lipofectamine 2000 and incubated for 48 hrs. Following the incubation, media was exchanged for growth medium with 10μM Trimethoprim or vehicle control and further incubated for 24 hrs. Media was collected and the undiluted samples or samples diluted 4, 16, 256, 1024, 4096 or 16384-fold were tested using human IL15 ELISA. The stabilization ratio was defined as fold change in IL15 expression with ligand treatment compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. Stabilization ratio greater than 1 is desired. Average IL15 ELISA readings and stabilization ratio are presented in Table 20.

Table 20: DD-IL15 induction

Media dilution (fold)	Vehicle	10 μM TMP	Stabilization ratio
1	0.396	0.820	2.073
4	0.154	0.287	1.867
16	0.074	0.116	1.567
64	0.056	0.073	1.301
256	0.053	0.057	1.075
1024	0.053	0.048	0.910
4096	0.049	0.049	0.995
16384	0.050	0.049	0.994

[00570] The 16-fold, 4-fold diluted, and undiluted media samples showed stabilization ratio greater than 1.5, suggesting a Trimethoprim dependent stabilization of IL15 at these dilutions.

Example 6. DD regulated expression of IL15-IL15Ra fusion molecule

[00571] A fusion molecule is generated by fusing membrane bound IL15, IL15 Receptor alpha subunit (IL15Ra) and DDs such as ecDHFR (DD), FKBP (DD), or human DHFR (DD). These fusion molecules were cloned into pLVX-EF1a-IRES-Puro vector.

[00572] To test ligand dependent IL15-IL15Ra production, 1 million HEK-293T cells were plated in a 6-well plate in growth media containing DMEM and 10 FBS and incubated overnight at 37°C, 5% CO2. Cells were then transfected with 100ng of constitutive IL15-IL15Ra (OT-IL15-008) or DD linked IL15-IL15Ra (OT-IL15-006, OT-IL15-007, OT-IL15-009, OT-IL15-010, OT-IL15-011) using Lipofectamine 2000 and incubated for 24 hrs. Following the incubation, media is exchanged for growth medium with or without 10μM Trimethoprim or 1μM Shield-1 and further incubated for 24 hrs. Cells were harvested and IL15 levels are analyzed via western blotting using human IL15 antibody (Abcam, Cambridge, UK). OT-IL15-009 showed the strong ligand (Trimethoprim) dependent stabilization of IL15, while OT-IL15-006 and OT-IL15-007 showed modest ligand dependent stabilization of IL15 (Figure 20A).

[00573] Surface expression of membrane bound IL15-IL15Ra constructs (OT-IL15-006, OT-IL15-007, OT-IL15-008, OT-IL15-009, OT-IL15-010, OT-IL15-011) was determined by FACS using anti-IL15 and anti-IL15Ra antibodies. HEK293T cells were transfected with IL15-IL15Ra constructs and then treated with suitable ligand (Shield-1 or Trimethoprim). 48 hours after transfection, cells were analyzed using FACS. As expected, constitutive IL15-IL15Ra construct OT-IL15-008 showed high surface expression of IL15 and IL15Ra both in the presence and absence of ligand. Consistent with the results from the western blot, OT-IL15-009 showed the strong ligand (Trimethoprim) dependent surface expression of IL15 and IL15Ra (Figure 20B, Figure 20C).

[00574] Membrane bound-IL15-IL15Ra constructs (OT-IL15-008 to OT IL15-011) were transduced into human colorectal carcinoma cell line, HCT-116 and stable integrants were selected with 2μg of puromycin. Stably integrated cells were then incubated for 24 hours in the presence or absence of 10μM Trimethoprim or 1μM Methotrexate.

[00575] Surface expression of IL15 -IL15Ra fusion constructs was examined by staining with PE- conjugated IL15Ra antibody (Cat no. 330207, Biolegend, San Diego, CA). The median fluorescence intensity obtained with the different constructs in the presence or absence of the corresponding ligand is presented in Table 21.

Table 21: Surface expression of IL15-IL15Ra fusion constructs

Construct	Median Fluorescence Intensity		
	DMSO	10μM TMP	1μM MTX
HCT-116 cells (control)	273		
OT-IL15-008 (Constitutive)	5315	7019	
OT-IL15-006 (ecDHFR (R12Y, E129K)	764	2978	
OT-IL15-010 (hDHFR (Y122I, A125F))	2657	5775	15864
OT-IL15-011(hDHFR (Q36F, N65F, Y122I))	1560	4010	14509

[00576] The stabilization ratio was calculated as the fold change in GFP intensity in ligand treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilization ratio was calculated as the fold change in GFP intensity in the DD regulated constructs compared to the constitutive construct (OT-IL15-008) in the absence of the ligand. Destabilization ratios less than 1 and stabilization ratios greater than 1 are desired in DDs. The ratios are presented in Table 22.

Table 22: IL15-IL15Ra destabilization and stabilization ratios

Construct	Destabilization ratio	Stabilization ratio	
		TMP	MTX
OT-IL15-008 (Constitutive)	19.47	1.32	
OT-IL15-006 (ecDHFR (R12Y, E129K)	0.14	3.90	-
OT-IL15-010 (hDHFR (Y122I, A125F))	3.48	2.17	5.97
OT-IL15-011(hDHFR (Q36F, N65F, Y122I))	0.59	2.57	9.30

[00577] Destabilization ratios less than one was observed with OT-IL15-006 (ecDHFR (R12H, E129K)) and OT-IL15-011(hDHFR (Q36F, N65F, Y122I)) indicating a strong destabilization in the absence of ligand. Stabilization ratio greater than 1 was observed with all constructs with TMP treatment and with both OT-IL15-010 and 11 with MTX treatment. These data show that OT-IL15-006 and OT-IL15-011 are both strongly destabilized in the absence of ligand and strongly stabilized in the presence of ligand.

[00578] The expression and ligand-dependent stabilization of IL15-IL15Ra constructs (OT-IL15-008 to OT-IL15-011) was measured in HCT-116. Cells were incubated with 10μM Trimethoprim or 1μM Methotrexate or DMSO for 24 hours. Following incubation, cells were harvested and cell extracts were prepared. Cell extracts were run on SDS-PAGE and western blotted with anti-IL15 antibody (Catalog No. 7213, Abcam, Cambridge, UK). As shown in Figure 20D, the IL15/IL15Ra constitutive construct (OT-IL15-008) showed ligand independent IL15 expression while the DD regulated constructs (OT-IL15-009 to OT-IL15-011) showed ligand dependent IL15 expression. The identity of the IL15 bands was also confirmed by immunoblotting with the anti-human DHFR antibody (Catalog No. 117705, Genetex, Irvine, CA). As shown in Figure 20D, both IL15-IL15Ra fusion constructs (OT-IL15-010 and 011) showed ligand dependent expression of DHFR expression.

[00579] To evaluate the dose dependence of ligand induced stabilization, IL15-IL15Ra fusion constructs namely, OT-IL15-009 (ecDHFR (R12Y, Y100I)), OT-IL15-010 (hDHFR (Y122I, A125F)), and OT-IL15-011 (hDHFR (Q36F, N65F, Y122I)) were stably transduced into HCT-116 cells and incubated with increasing concentrations of Trimethoprim for 24 hours. Surface expression of IL15-IL15Ra fusion construct was quantified by FACS using IL15Ra- PE antibody. The median fluorescence intensity with increasing doses of TMP is represented in Table 23.

Table 23: Surface expression of IL15-IL15Ra

Dose (μM)	Median Fluorescence Intensity		
	ecDHFR (R12Y, 100I)	hDHFR (Y122I, A125F)	hDHFR (Q36F, N65F, Y122I)
DMSO	1260	3034	2357
0.01	1384	2791	2291
0.02	1492	2833	2216
0.05	1947	2924	2054
0.14	2741	2740	2150
0.41	3360	2817	2400
1.23	4014	2890	2251
3.7	4265	3117	2494
11.11	4267	3473	2841
33.33	4485	4019	3409
100	4633	5227	4592

[00580] As shown in Table 23, all three constructs showed a dose dependent increase in median fluorescence intensity indicating a dose dependent increase in surface expression of IL15-IL15Ra fusion upon addition of DD stabilizing ligand.

[00581] The time course of ligand dependent stabilization of IL15-IL15Ra fusion constructs was measured in HCT-116 cells. Cells were transduced with OT-IL15-009 (ecDHFR (R12Y, Y100I) construct and incubated with 10μM Trimethoprim for 0, 12, 16, 24, 48 or 72 hours. Following incubations, surface expression of IL15-IL15Ra fusion construct was quantified by FACS using IL15Ra- PE antibody and compared to parental untransfected cells. The median fluorescence intensity (MFI) over time is represented in Table 24.

Table 24: Time course of IL15-IL15Ra surface expression

Time (hours)	MFI
Parental	3054
0	4004
12	7054
16	9390
24	14056
48	28644
72	35303

[00582] As shown in Table 24, OT-IL15-009 (ecDHFR (R12Y, Y100I) showed a time-dependent increase in median fluorescence intensity indicating that the surface expression of IL15-IL15Ra fusion increased with increased duration of treatment with DD stabilizing ligand.

Example 7. DD regulated CD19 CAR expression

[00583] A CD19 CAR fusion polypeptide was linked to either FKBP-DD, ecDHFR -DD or human DHFR- DD and the constructs were cloned into pLVX-IRES-Puro vector.

[00584] FKBP, ecDHFR and hDHFR DDs were positioned either between the CD19 scFv and the CD8αhinge (OT-CD19C-002, OT-CD19C-003), between the CD8αhinge and the transmembrane domain (OT-CD19C-004, OT-CD19C-005) or at the C terminus of the construct (OT-CD19C-007, OT-CD19C-008, OT-CD19C-009, OT-CD19C-010, OT-CD19C-011). In some instances, a furin cleavage site was added between the DD and the CD19 scFv. A constitutively expressed CAR construct, OT-CD19C-001 was used as a positive control.

[00585] To test ligand dependent expression of DD-CD19 CAR constructs, 1 million HEK 293T cells were cultured in growth medium containing DMEM and 10% FBS and transfected with CAR constructs using Lipofectamine 2000. 48 hours after transfection, cells were treated with 1μM or10μM Shield-1, 10μM Trimethoprim, 1μM Methotrexate, or vehicle control and incubated for 24 hours. Cells were harvested, lysed and immunoblotted for CD3 Zeta, a component of the CAR, using anti-CD247 (BD Pharmingen, Franklin Lanes, NJ) and Alexa 555-conjugated-goat-anti mouse antibody (red) (Li-Cor, Lincoln, NE). Lysates were also immunoblotted for Actin with Alexa 488-conjugated secondary antibody (green) to confirm

uniform protein loading in all the samples. Compared to the untreated control, OT-CD19C-002 and OT-CD19C-003 showed increased levels of CD3 Zeta in the presence of ligands Shield-1 and TMP respectively indicating the stabilization of the CD19 CAR (Figure 21A). As shown in Figure 21B, OT-CD19C-008 and OT-CD19C-010 constructs showed strong increase in CD3 Zeta levels in the presence of Methotrexate and low levels in the absence of ligand, indicating a strong ligand-dependent stabilization of CD19 CAR. OT-CD19C-007 and OT-CD19C-009 showed modest increase in CD3 Zeta levels in the presence of Shield-1 and Methotrexate respectively, indicating a modest ligand-dependent stabilization of CD19 CAR. As expected, the constructively expressed, OT-CD19C-001 showed strong expression of CD19 CAR in the absence of ligand treatment.

[00586] Lysates from cells expressing CD19 CAR constructs were also immunoblotted for 4 1-BB, a component of the CAR. As shown in Figure 21C, OT-CD19C-008, OT-CD19C-009, OT-CD19C-010 and OT-CD19C-011 showed low levels of 4-1 BB in the absence of ligand and high levels of 4-1 BB in the presence of the ligand, Methotrexate, indicating a strong ligand dependent stabilization of CD19 CAR using these constructs. OT-CD19C-003, OT-CD19C-006 and OT-CD19C-007 showed modest increase in 4-1BB expression levels with treatment of corresponding ligands- TMP and Shield-1, indicating a modest ligand dependent stabilization of CD19 CAR. Constructs OT-CD19N-014 and OT-CD19N-015, which contain a furin cleavage site, showed an additional, smaller 4 1BB sized protein product upon treatment with MTX. This smaller sized 4-1BB protein band was only seen with the addition of the ligand and its molecular weight is consistent with the size of the CD19 CAR in OT-CD19-001. These data indicate that the furin cleavage occurs only with ligand treatment.

[00587] Surface expression of DD-CD19 CAR constructs in HEK 293T cells was measured using Fluorescence activated cell sorting (FACS) with Protein L-Biotin-Strepavidin-Allophycocyanin which binds to the kappa light chain of the CAR (ThermoFisher Scientific, Waltham, MA). Cells were treated with 1μM Shield-1, 1μM Methotrexate,10μM Trimethoprim or vehicle control for 24 hours and subject to FACS analysis. As shown in Figure 21D, surface expression of OT-CD19C-002 with FKBP-DD was detected only in the presence of Shield-1, while OT-CD19C-003 with ecDHFR-DD showed surface expression only in the presence of Trimethoprim. As expected, constitutively expressed construct OT-C19C-001 showed high expression both in ligand and control vehicle treated cells. Additional constructs were analyzed by FACS with Protein L-Biotin-Strepavidin-Allophycocyanin in a separate experiment. The percentage of GFP positive cells obtained with each construct in the presence or absence of ligand is presented in Table 25. In Table 25, N/A indicates not applicable.

Table 25: Percentage GFP positive cells

Construct	Ligand	Percentage GFP positive cells	
		No Ligand	Ligand
OT-CD19C-001	N/A	46.8	45.4
OT-CD19C-006	TMP	46.6	43.6
OT-CD19C-007	Shield-1	28.9	34
OT-CD19C-008	MTX	15.8	31.3
OT-CD19C-009	MTX	16.5	34.2
OT-CD19C-010	MTX	14.8	33
OT-CD19C-011	MTX	14.5	32.9
OT-CD19C-012	TMP	19.1	18.7
OT-CD19C-013	Shield-1	0.91	0.4
OT-CD19C-014	MTX	4.68	16.2
OT-CD19C-015	MTX	3.04	18.2

[00588] An increase in the percentage GFP positive cells was observed with OT-CD19C-007, OT-CD19C-008, OT-CD19C-009, OT-CD19C-010, OT-CD19C-011, OT-CD19C-014, and OT-CD19C-015. The highest increase in the percentage of GFP positive cells was observed with OT-CD19C-014, and OT-CD19C-015 constructs.

[00589] The mean fluorescence intensities are presented in Table 26. In Table 26, MFI represents mean fluorescence intensity. The stabilization ratio was calculated as the fold change in GFP intensity in ligand treated samples compared to treatment with DMSO (i.e. in the absence of ligand) with the same construct. The destabilization ratio was calculated as the fold change in GFP intensity in the DD regulated constructs compared to the constitutive construct (OT-CD19C-001) in the absence of the ligand. Destabilization ratios less than 1 and stabilization ratios greater than 1 are desired.

Table 26: CD19 CAR surface expression

Construct	Ligand	MFI		Destabilization Ratio	Stabilization Ratio
		No Ligand	Ligand		
OT-CD19C-001	N/A	453	407		0.90
OT-CD19C-006	TMP	425	325	0.94	0.76
OT-CD19C-007	Shield-1	132	123	0.29	0.93
OT-CD19C-008	MTX	89.4	148	0.20	1.66
OT-CD19C-009	MTX	93.3	200	0.21	2.14

OT-CD19C-010	MTX	85.6	160	0.19	1.87
OT-CD19C-011	MTX	83.3	172	0.18	2.06
OT-CD19C-012	TMP	112	105	0.25	0.94
OT-CD19C-013	Shield-1	61	49.5	0.13	0.81
OT-CD19C-014	MTX	78.6	124	0.17	1.58
OT-CD19C-015	MTX	73.3	143	0.16	1.95

[00590] A destabilization ration less than 1 was observed with all constructs indicating that all DD regulated constructs are destabilized in the absence of ligand. A stabilization ratio of greater than 1 was observed with OT-CD19C-008, OT-CD19C-009, OT-CD19C-010, OT-CD19C-011, OT-CD19C-014 and OT-CD19C-015. Notably, these constructs were also destabilized in the absence of ligand and therefore represent suitable CD19-DD constructs.

Example 8. *In vitro* T cell assay development

[00591] The goal of the study was to determine the T cell stimulation regimen and dose of IL12 needed to maximize T cell persistence and T cell differentiation *in vitro*. The study recapitulates the design of the adoptive cell therapy regimen wherein the T cells were initially exposed to the antigen *in vitro* which results in activation followed by a resting phase and finally *in vivo* transfer where the T cells encounter the antigen again. T cells were stimulated CD3/CD28 beads or soluble CD3/CD28 on day 0 and the CD3/CD28 stimulus was washed off at the end of 48 hours. Cells were treated with a dose of IL12 ranging from 0.01- 1000 ng/mL. On day 9, the Th1 phenotype of the cells was evaluated by examining the frequency of IFNgamma positive CD4+ cells and CD8+ cells. On day 14, cells were divided into two groups- one group received a second CD3/CD28 stimulation and a second group that was not stimulated. On day 16, the Th1 phenotype was evaluated in both groups using FACS. The results for day 16 are presented in Figure 22. IFN gamma expression was higher in cells that received a CD3/CD28 restimulation on day 14 compared to cells that did not receive second stimulation. This indicates that both antigen restimulation and IL12 exposure were required for the Th1 phenotype. Further, as little as 0.1 ng/mL of IL12 was able to cause Th1- skewing and IFN gamma production from T cells *in vitro*, and higher doses of IL12 further improved this effect.

Example 9. Measuring human T cell responses *in vitro* and *in vivo*

[00592] IL12 promotes the differentiation of naïve T cells into Th1 cells which results in the secretion of IFN gamma from T cells. Human T cells were treated with IL12 or left untreated and analyzed by flow cytometry for the expression of IFN gamma and T cell marker CD3.

Treatment with IL12 resulted in the differentiation of T cells as measured by an increase in the percentage of IFN gamma positive T cells from 0.21 to 22.3 (see inset of Figure 23A).

[00593] To test if membrane bound IL15/IL15Ra fusion protein (OT-IL15-008) can induce human T cell expansion, human T cells were transduced with the construct. T cell proliferation was measured by evaluating forward and side scatter of the T cell population using flow cytometry. Transduction with membrane bound IL15/IL15Ra fusion construct resulted in the expansion of human T cells (58.9) compared to control untransfected cells (37.8) (Figure 23B).

[00594] Tracking T cells following their adoptive transfer is critical to determine their distribution at different sites in the host, their identity and persistence over time. Human T cells were stimulated with CD3/CD28 beads and incubated with 50U/ml of IL2. Cells were expanded *in vitro* for 7 days with IL2 supplementation on day 3 and day 5. On day 5, the CD3/CD28 beads were removed and the cells were cultured for two days. On day 7, cells were washed to remove IL2 and 5 million human T cells were injected intravenously into immune compromised, NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice. Blood samples were obtained 4, 24, 120 and 168 hours after cell transfer. Mice were euthanized 168 hours after cell transfer and the bone marrow and spleen were harvested. Immune cells were isolated from all samples and analyzed for the presence of human T cells using CD3 and CD45 cell surface markers. As shown in Figure 23C, the percentage of CD3 positive, CD45 positive human T cells in the blood was higher in animals injected with human T cells, especially at 120 and 168 hours. CD3 positive, CD45 positive human T cells were also detected in the spleen and bone marrow of animals injected with human T cells. As expected no CD3 positive, CD45 positive human T cells were detected in control animals that were not injected with human T cells.

[00595] To determine the identity of the T cells following adoptive transfer, blood samples were collected from mice 48 hours after injection. CD4 and CD8 T cells were analyzed for surface expression of CD45RA and CD62L. Both markers are highly expressed in naïve T cells but are lost as the T cells become antigen exposure. As shown in Figure 23D, human CD4 and CD8 T cells showed high surface expression of both markers prior to injecting into mice, but was lost 48 hours after *in vivo* cell transfer indicating that the human T cells are exposed to the antigen *in vivo*.

Example 10. DD regulated IL12 mediated functions

[00596] DD-IL12 function is characterized *in vivo* by evaluating the ability of tumor cells expressing these constructs to establish tumors and proliferate under the treatment of corresponding synthetic ligands e.g. Shield-1, Trimethoprim or Methotrexate. 2-10 million HCT-116 cells stably transduced with the constructs are subcutaneously xenografted with 50 matrigel

into mice capable of producing functional B and NK cells. Approximately, two weeks after injection, when the tumors reach a size of approximately 300 cubic mm, mice are dosed with corresponding stabilizing ligands e.g. Shield-1, Trimethoprim or Methotrexate at varying concentrations every two days. Shield-1 is injected with a carrier consisting of 10 Dimethylacetamide, 10 Solutol HS15, and 80 saline. Tumor volume and body weight are monitored twice a week and the experiment is terminated once the tumors reach 1000 cubic mm in size. Plasma and tumor samples are collected 8 hours after the last dose of the ligand andIL12 as well as the ligand levels are measured.

[00597] To evaluate the ability of IL12 expressing cells to form tumors, HCT-116 cells stably transduced with DD-IL12 constructs are pretreated with corresponding stabilizing ligands, Shield-1, Trimethoprim or Methotrexate and subsequently xenografted into mice. Reduction in tumor growth and a concomitant increase in IL12 levels in ligand treated mice compared to untreated controls is indicative conditional regulation of IL12 *in vivo*.

Example 11. DD regulated recombinant IL12 mediated functions in T cells

[00598] Functional responses to DD-IL12 is evaluated in primary human T cells and in human cell lines/transformed hematopoietic cell lines e.g. Raji cells. Human T cells are purified from peripheral blood mononuclear cells (PBMCs) by negative selection using CD4+ T- cell isolation kit (Miltenyi Biotec, Germany). T cells are treated with growth media from HEK 293T cells expressing DD-IL12 constructs for 5 days. Cells are then activated with beads conjugated with-CD3/CD28 beads (Thermo Fisher Scientific, Waltham, MA) at the ratio of 3 beads per T cell and cultured for 3 days. Functional response to DD-IL12 is determined by measuring Interferon gamma in CD3 positive cells using flow cytometry following treatment with ligand or vehicle control. IL12 promotes the differentiation of naïve T cells into Th1 cells which results in the secretion of IFN gamma from T cells.

[00599] To evaluate IL12 induced phosphorylation of STAT4 (Signal transducer and activator of transcription 4), human T-cells are isolated from PBMCs and activated with phytohemagglutinin (PHA, 2μg/ml) for 3 days followed by treatment with 50 IU/ml of Interleukin 2 (IL2) for 24hrs. Cells are then washed, resuspended in fresh media and rested for 4 hrs in the presence of ligand or vehicle control. Supernatant from DD-IL12 expressing HEK293T cells is added to the primary cells, followed by incubation for 30 minutes. Cells are then harvested and STAT4 phosphorylation is analyzed using STAT4 antibody (Cell Signaling Technology, Danvers, MA).

Example 12. Functional analysis of DD regulated IL15-IL15Ra fusion molecule

[00600] Activation via IL15 can sustain T cell persistence by conferring a survival advantage. In addition, IL15/IL15Ra fusion molecule has been shown to confer a memory phenotype on T cells and increase proliferation of NK cells (Hurton (2016), PNAS, 113: E7788-7797; the contents of which are incorporated herein by reference in their entirety).

[00601] To evaluate signaling by DD regulated IL15-IL15Ra fusion constructs, NK-92 cells are incubated with HCT-116 cells expressing DD regulated IL15-IL15Ra fusion constructs. Trans signaling by IL15/IL15Ra is expected to increase STAT5 phosphorylation in NK92, which is measured by western blotting, and by FACS. Proliferation of NK92 cells is also measured.

[00602] To evaluate the effect of DD regulated IL15-IL15Ra fusion constructs on primary T cells, cells are transduced with the fusion constructs. T cell proliferation in the absence of exogenous IL15 supplementation is measured. The T cell memory phenotype is measured by quantifying CD62L expression by FACS.

[00603] To assess if DD-IL15/IL15R expressing T cells maintain prolonged persistence *in vivo*, DD modified T cells are injected into mice. Constructs are tagged with luciferase reporter to allow *in vivo* tracking in mice. Mice are treated with vehicle control or corresponding ligand, Shield-1, Trimethoprim or Methotrexate depending on the construct utilized and monitored over a period of 40-50 days using bioluminescent imaging (PerkinElmer, Massachusetts). Mice treated with ligand are expected to retain T cells expressing DD-IL15/IL15Ra while T cells in vehicle control treated animals are not expected to persist.

Example 13. DD regulated CD19 CAR expression and function in T cells

[00604] Ligand dependent expression of DD-CD19 CAR constructs is evaluated in primary human T cells and in immortalized/transformed hematopoietic cell lines e.g. Raji cells, Jurkat cells and K562 cells. Human T cells are purified from peripheral blood mononuclear cells (PBMCs) by negative selection using CD4+ T- cell isolation kit (Miltenyi Biotec, Germany). Primary T cells and hematopoietic cell lines are stably transduced with DD-CD19 CAR constructs. Cells are treated with 10μM Shield-1, 10μM Trimethoprim, 1μM Methotrexate or vehicle control and immunoblotted for CD3 Zeta using anti CD247 antibody.

[00605] The production of functional DD-CD19 CAR is analyzed in primary human T cells or human cell lines (NALM6, K562, Jurkat and Raji cells). Cells are incubated with CD19 expressing antigen presenting cells or CD19/Fc fusion protein in the presence of DD stabilizing ligands Shield-1, TMP or MTX. After incubation, cells are stained with fluorescently labelled anti-CD69 antibodies and analyzed by flow cytometry. Cells with high CD69 expression are considered to have a functional DD-CD19 CAR. Functional response to DD-CD19 CAR is also

determined by measuring interferon gamma levels using ELISA. DD-CD19 CAR expressing cells are expected to demonstrate higher Interferon gamma levels in the presence of ligand than untreated cells.

[00606] Cytolytic potential of DD-CD19 CAR expressing cells is evaluated in primary human T cells or human cell lines (e.g. NALM6, K562 and Raji) using Chromium-51 Release Assay. Target cells are loaded with of $Na_2\,^{51}CrO_4$, washed twice and resuspended in phenol red-free growth medium. Untreated or ligand treated DD-CD19 CAR and mock transduced cells are coincubated with CD 19 expressing target cells at various effector: target cell ratios, and chromium release into the supernatant is measured using a liquid scintillation counter. Cells with DD-CD19 CAR are expected to demonstrate specific cytolysis only in the presence of ligand. Cells with DD-CD19 CAR in the absence of ligand or mock transfected cells are expected to show minimal cytolytic activity.

[00607] The *in vivo* antitumor efficacy of DD-CD19 CAR is also evaluated. Immune compromised mice are injected with luciferase expressing human leukemic cell lines (NALM-6). Subsequently, mice are injected with DD-CD19 CAR T cells via tail vein injections. Mice are subdivided into treatment groups and are treated with a range of ligand doses. Two control groups are also included in the study: a control group that did not receive any ligand and another group that did not receive any T cells. Tumor burden as measured by luciferase activity is monitored over time using bioluminescent imaging. Mice treated with DD-CD19 CAR T cells and ligand are expected to have a reduced tumor burden when compared to control animals.

Example 14. Evaluation of antitumor response of DD regulated payloads in syngeneic mouse models

[00608] The efficacy of cancer immunotherapy in organisms with intact immune cells is evaluated using syngeneic mouse models e.g. pMEL-1 and 4T1 mouse models. Immune cells such as T cells and NK cells are isolated from syngeneic mice and transduced with DD regulated payloads such as DD-IL12, DD-IL15, DD1L15-IL15Ra, and DD-CD19 CAR,. Cells are then injected into mice bearing subcutaneous syngeneic tumors and treated with varying concentrations of ligand, Shield-1, Trimethoprim or Methotrexate, depending on the DD used. Mice treated with immune cells transduced with DD regulated payload are expected to have a reduced tumor burden when compared to control animals.

Example 15. Optimizing workflow for discovery of DD-regulated immunotherapeutic agents

[00609] To identify DD-CD19 CAR constructs suitable for immunotherapy, constructs are introduced into cell lines e.g. HEK293T cells and Jurkat cells. The expression of the construct in

the presence or absence of the corresponding ligand is tested. Constructs which show low basal expression in the absence of ligand and robust, ligand-dose responsive expression are selected for further analysis. If no DD-CD19 CAR constructs show ligand-dependent expression, then constructs are redesigned and the experiment is repeated till a regulatable construct is identified. Next, the ligand dependent regulation of the DD-CD19 CAR constructs is tested *in vitro* in primary T cells. If the constructs show low basal expression in the absence of the ligand and ligand dose responsive expression, they are subject to *in vivo* PK/PD proof of concept experiments. Otherwise, the constructs are redesigned and the new constructs are subject to similar analysis. The constitutively expressing CD19 CAR constructs are transduced into T cells and CD19 CAR expression is measured in parallel to the regulated construct. If no expression is detected in vitro, efforts are refocused on testing DD- CD19 CAR constructs *in vitro* in T cells. In contrast, if the constitutive constructs show expression, then the expression of CD19 CAR is measured *in vivo*.

[00610] To test in vivo PK/PD, mice are injected with T cells expressing DD-CD19 CAR constructs and the test group is dosed with the ligand corresponding to the DD, while the control group is dosed with the appropriate vehicle control. Constructs that display ligand-dependent expression of CD19 CAR are selected for in vivo functional proof of concept experiments. Parallel experiments are also conducted using the constitutive CD19 CAR constructs. If constitutive CD19 CAR expression is detected *in vivo*, then the constructs are selected for functional experiments. If no expression is detected *in vivo*, then constructs are redesigned.

[00611] Functional analysis *in vivo* is performed by testing if the constitutive and DD regulated CD19 CAR expressing T cells display anti-tumor activity in a constitutive or ligand dependent manner respectively. If yes, then *in vivo* proof of concept is achieved and constructs suitable for immunotherapy are identified. If none of the DD regulated constructs show anti-tumor activity, then alternate dosing regimens are explored. If the constitutive CD19 CAR constructs do not show anti-tumor activity, then efforts are focused on identifying DD-CD19 CAR constructs that show in vivo expression in T cells.

Example 16. Co-expression of DD regulated payloads

[00612] Toxicity related to systemic administration of interleukins can be circumvented by using CAR-T cells to deliver interleukins to the target tissue. This combinatorial approach also has greater anti-tumor activity than interleukin and CAR therapy alone. Cells are co-transfected with CD19 CAR (constitutive or DD regulated) and DD-Interleukin e.g. DD-IL12, DD-IL15 and DD-IL15/IL15Ra constructs. Transfected cells are treated with stabilizing ligands depending on

the DD utilized. CD19 CAR expression is evaluated by immunoblotting for CD3 zeta. DD-IL12, DD-IL15 and DD-IL15/IL15Ra expression in the media is measured by ELISA.

Example 17. CAR expression and functionality in T cells

[00613] Primary T cells were transduced with CD19 CAR constructs. Surface expression of CD19 CAR construct was measured using Fluorescence activated cell sorting (FACS) with Protein L-Biotin-Strepavidin-Allophycocyanin which binds to the kappa light chain of the CAR (ThermoFisher Scientific, Waltham, MA). To determine the percentage of the CD4 and CD8 sub populations of CAR T cells, cells were analyzed by anti CD4, anti CD8 antibodies and Protein L. As shown in Figure 24A, 67.3 % of CAR positive cells obtained were CD4 positive, while only 14.2% cells were CD8 positive.

[00614] To test the ability of CD19 CAR cells to kill target cells, primary T cell populations transduced with OT-CD19N-001 or OT-CD19N-017 were cocultured with K562 cells expressing CD19 (target cells) at a ratio of 5:1. Additional control combinations of T cells and target cells were also set up. These included CAR expressing T cells co cultured with K562 cells, T cells co cultured with K562 cells expressing CD19 and K562 cells expressing CD19 without T cell co culture. K562 cells were fluorescently labelled with NucLight Red and co cultured with T cells for 30 hours. Cell death was monitored by labelling cells with Annexin V and K562 target cell death was measured by evaluating Annexin V staining in NucLight Red positive cells. The ratio of Annexin V staining per target cell area was calculated. As shown in Figure 24B, OT-CD19N-001 or OT-CD19N-017 expressing T cells were effective in killing target K562 cells expressing CD19. A low level of target cell killing was observed when untransduced T cells were cocultured with CD19 expressing target cells. As expected, cell death was minimal in the co-culture of OT-CD19N-001 expressing T cells and K562 cells (without CD19 expression). These data show that CD19 CAR cells are effective in killing their corresponding target cells.

Example 18. Regulated expression of IL15-IL15Ra in T cells

[00615] DD regulated IL15-IL15Ra constructs such as OT-IL15-009 or constitutively expressed constructs such as OT-IL15-008 were transduced into T cells such as primary T cells or SupT1 cells. The transduction was carried out at two different lentivirus concentrations, 5 µl and 20 µl for the DD regulated construct using Lentiboost ™ (Sirion Biotech, Germany). 4 days after transduction, cells were treated with 10µM TMP or DMSO control for 24 and 48 hours. Samples were analyzed with an anti IL15Ra antibody using FACS. Additional controls samples such as cells treated with Lentiboost only, untransduced cells treated with DMSO or TMP, and Isotype

controls were included in the FACS analysis. The FACS results are depicted in Figure 25A for 24 hours of TMP treatment and in Figure 25B for 48 hours of TMP treatment. In both figures, DMSO-A and TMP-A indicate cells treated with 5 µl of lentivirus and DMSO- B and TMP-B indicate cells treated with 20 µl of lentivirus. Treatment of T cells expressing OT-IL15-009 with TMP for 24 hours resulted in an increase in the expression of IL15Ra in T cells with both doses of lentivirus used. Additionally, very low levels of IL15Ra were detected in the DMSO treated samples under the same conditions as well as in untransduced T cells. As expected, the constitutively expressed construct, OT-IL15-008 showed high expression of IL15Ra. TMP dependent expression of OT-IL15-009 was not observed in SupT1 cells (Figure 25A). Similar results were observed for both T cells and SupT1 cells at 48 hours (Figure 25B). These results show that tight regulation of IL15-IL15Ra constructs can be achieved in primary T cells.

[00616] The surface expression of IL15 and IL15Ra was measured for OT-IL15-008 and OT-IL15-009. The percentage of cells expressing IL15, IL15Ra or both on the cell surface is presented in Table 27.

Table 27: Surface expression of IL15 and IL15Ra

	% Positive cells	
	OT-IL15-008	OT-IL15-009
IL15 and IL15Ra positive	2.03	0.51
IL15Ra positive	13.0	15.8
IL15 positive	0.29	0.60

[00617] As shown in Table 27, the percentage of cells with detectable surface expression of IL15 and IL15Ra was less than 5% with both constructs. Further, the percentage of cells with surface expression of IL15Ra was much higher than the percentage of cells with detectable surface expression of IL15.

[00618] The effect of increasing doses of TMP on IL15Ra expression in T cells was measured using the OT-IL15-009 construct. T cells were treated with a range of doses of TMP starting from 0.156 µM to 160 µM for 24 hours. IL15Ra expression was measured using FACS. As shown in Figure 25C, the percentage of IL15Ra expressing T cells with OT-IL15-009 cells was detected even at the lowest concentration of TMP and the percentage of IL15Ra positive cells at the lowest concentration of TMP was higher than the untreated control. The percentage of IL15Ra cells increased with increasing doses of TMP.

Example 19. TMP dose responsive expression of IL15-IL15Ra

[00619] IL15-IL15Ra fusion constructs, OT-IL15-008, OT-IL15-009, and OT-IL15-010 were stably expressed in HCT116 cells treated with increasing doses of TMP ranging from 10μM, 33μM, and 100μM TMP for 24 hours. Cell lysates were immunoblotted with anti IL15Ra antibody. As shown in Figure 26, IL15Ra expression of OT-IL15-009 was virtually undetectable in the absence of TMP, and addition of increasing doses of TMP resulted in an increase in IL15Ra levels. Modest increase in IL15Ra expression was observed with OT-IL15-010 construct with the addition of TMP. As expected, the constitutive construct, OT-IL15-008 showed strong expression of IL15Ra both in the presence and absence of ligand.

Example 20. Effect of IL15-IL15Ra on T cell persistence and T cell memory phenotype

[00620] The effect of constitutively expressed IL15-IL15Ra fusion construct, OT-IL15-008 on T cell persistence was measured in NSG mice. T cells were transduced with OT-IL15-008 and 4 million cells T cells were injected intravenously into NSG mice (number of mice =3). As a control, additional mice were injected with untransduced T cells. Blood samples were obtained from mice at 2, 3, 4, 5 and 6 weeks after injection and analyzed by FACS for the presence of CD8 and/or CD4 positive human T cells expressing IL15 and IL15Ra. The percentage of human T cells in the blood was calculated as the percentage of total T cells i.e. human T cells (measured using anti-human CD45 antibody) and the mouse T cells and endothelial cells (measured using the anti-mouse CD45 antibody). As shown in Figure 27 A, the percentage of T cells in the blood at 2 weeks was greater in mice injected with T cells transduced with OT-IL15-008 compared to control mice that were injected with untransduced T cells. This observed increase in T cells decreased over 3,4, and 5 weeks, and the percentage of T cells was comparable between the two cohorts. At 6 weeks, one of the mice injected with OT-IL15-008 transduced T cells showed a higher percentage of human T cells in the blood. Thus, at 2 weeks, the frequency of human T cells in the blood is increased in the blood of mice injected with OT-IL15-008 transduced T cells.

[00621] The number of T cells in the blood was measured by comparing the number of human T cells in 50 uL of mouse blood using anti-human CD45 antibody as a marker for human T cells and anti-murine CD3 antibody as a marker for murine endothelial cells. As shown in Figure 27B, the number of human T cells in the blood increased at 2 weeks in mice injected with OT-IL15-008 transduced T cells, as compared to mice injected with untransduced T cells. The difference between the two cohorts was diminished at 3 weeks and 4 weeks. At 6 weeks, one of the mice injected with OT-IL15-008 transduced T cells showed a higher number of human T cells in the

blood. Thus, at 2 weeks, the frequency and number of human T cells in the blood is increased in the blood of mice injected with OT-IL15-008 transduced T cells. These data support the role of IL15-IL15Ra fusion proteins in T cell persistence. The increased T cell frequency and number observed at 6 weeks in one of the mice may be due to graft versus host disease.

[00622] The effect of OT-IL15-008 expression on the CD4 and CD8 subset of T cells was measured prior to injecting into mice (Week 0) and 2 weeks after injection. As shown in Figure 27C, the ratio of CD4 and CD8 cells was 1:1 prior to injecting into mice. However, at 2 weeks, the proportion of CD4 positive cells was much higher than the CD8 positive cells in the transduced cells, indicating that OT-IL15-008 causes a preferential expansion of CD4 positive cells. The expression of the OT-IL15-008 construct within the CD4 and CD8 subsets was measured using anti IL15Ra antibody. As shown in Figure 27D, prior to injections, 25 % of the OT-IL15-008 transduced CD4 T cells and CD8 T cells expressed IL15Ra. At week 2, the percentage of IL15Ra positive CD4 and CD8 T cells increased to 80% indicating a preferential expansion of T cells transduced with OT-IL15-008. As expected, untransduced control T cells were negative for IL15Ra expression.

Example 21. IL12 dependent, re-stimulation independent Th1 markers

[00623] T cells require T cell receptor restimulation *in vivo* or *in vitro* stimulation with CD3/CD28 to produce IFNgamma. To study the effect of IL12 activity on T cells in the absence of restimulation, several T cell markers were explored. T cells were expanded using one of the following 4 expansions strategies (i) Day 10 cytokine switch from IL2 to IL12, CD3/CD28 stimulation from day 0 to day10 with no restimulation (ii) Day 10 cytokine switch from IL2 to IL12, CD3/CD28 stimulation from day 0 to day 10 and restimulation at with CD3/CD28 from day 12 to day 14 (iii) Day 10 cytokine switch from IL2 to IL12, CD3/CD28 stimulation from day 0 to day3 with no restimulation (iv) Day 10 cytokine switch from IL2 to IL12, CD3/CD28 stimulation from day 0 to day 3 and restimulation at with CD3/CD28 from day 12 to day 14. Markers tested include CD69, IFNg, Perforin, CXCR3, Granzyme B, CCR5, CXCR6, Ki-67 and T-bet. IFNg appears to be the most robust and consistent marker for IL12 activity on human T cells, but requires re-stimulation of T cells to induce production. Th1 markers which increase in response to IL12 in the absence of re-stimulation and IL2 (likely in vivo conditions) include Ki-67, T-bet, Perforin, CXCR3, and CCR5.

Example 22. Effect of cytokines on NK cell proliferation and activation

[00624] Immune cells such as Natural Killer cells depend on cytokines such as IL15 for their proliferation and survival. This dependence on cytokines can be used to test the functionality of DD regulated or constitutively expressed cytokines and cytokine fusion proteins.

[00625] The dependency of the NK-92 cells on cytokines for activation was tested. Cells were initially cultured for 3 days with IL2, following which, cells were washed twice and cultured in media without IL2 for 7 hours. The cells were cultured for 18 hours in the presence of IL12 (10 ng/ml) or varying concentrations of IL15 (100 ng/ml, 20 ng/ml, 4 ng/ml, 0.8 ng/ml, 0.16 ng/ml, 0.032 ng/ml, 0.0064 ng/ml and 0.00128 ng/ml). NK-92 cell activation in response to IL15 and IL12 treatment was evaluated by FACS analysis using a panel of markers whose increased expression is associated with NK cell activation. These markers include NKG2D, CD71, CD69; chemokine receptors such as CCR5, CXCR4, and CXCR3, Perforin, Granzyme B and Interferon gamma (IFNg). Prior to FACS analysis for IFNg, cells were cultured for 4 hours with Brefeldin A. NK cells respond to external stimuli such as cytokines in their environment through the phosphorylation of proteins JAK/STAT, ERK, and p38/MAPK pathways which are important for cell activation, signaling and differentiation pathways. The phosphorylation of AKT, STAT3 and STAT5 in response to cytokine addition was measured by FACS. Since phosphorylation events are transient NK-92 cells were treated with the cytokines for 15 or 60 minutes, prior to the analysis. The fold change in mean fluorescence intensities compared to untreated for IL15 treatment are presented in Table 28.

Table 28: IL15 induced markers

IL15 dose (ng/ml)	CD69	CXCR4	Perforin	Granzyme B	pSTAT5 (15 mins)	pSTAT5 (60 mins)	IFNgamma
100	1.91	3.87	1.67	1.48	1.98	2.34	9.00
20	2.10	3.62	1.57	1.40	1.96	2.35	5.55
4	1.59	3.03	1.28	1.16	1.81	2.35	2.76
0.8	1.18	2.10	1.16	1.09	1.76	2.17	1.92
0.16	0.99	1.41	1.04	1.03	1.44	2.08	2.41
0.032	1.05	1.14	0.92	0.92	1.23	1.67	0.95
0.0064	1.11	1.19	0.79	0.78	1.03	1.26	0.85
0.00128	1.07	1.15	0.85	0.88	0.99	1.04	1.19

[00626] Treatment with IL15 resulted in an increase in the expression of CD69, CXCR4, Perforin, Granzyme B, and IFNg. The effect of IL15 on these markers was dose dependent with a higher dose of IL15 resulting in a corresponding upregulation of markers. Phosphorylation of

STAT5 was increased both at 15 and 60 minutes after the addition of IL2 or IL15. Taken together, these results show that cytokines can activate NK cells.

[00627] The fold change in activation markers observed with IL12 treatment are shown in Table 29.

Table 29: IL12 induced markers

Marker	Fold change
CCR5	1.60
Perforin	1.67
Granzyme	1.87
IFNg	1.74
IFNg (supernatant)	666.15

[00628] Treatment with IL12 resulted in an increase in the expression of markers CD69, CCR5, Perforin, Granzyme B, and IFNgamma. Further, IFNg levels secreted by NK-92 cells into the media higher than untreated controls upon treatment with IL12. Treatment with IL2 resulted in an increase in the expression of CXCR4, Perforin, Granzyme B, and IFNg. Further, IFNg levels secreted by NK-92 cells into the supernatant was higher than untreated controls upon treatment with IL2.

Example 23. Effect of cytokines on T cell expansion and activation

[00629] To test the requirement of IL2 and IL12 for T cells expansion and activation, T cells were stimulated with soluble CD3/CD28, CD3/CD28 Dynabeads or left unstimulated for two days. Each of these groups was further split into two sub groups. One sub group was treated with IL2 and 100 ng/ml of IL12 while the second sub group was treated with IL2 only for the duration of the stimulation. For the soluble CD3/CD28 stimulated cells, a third subgroup that was only treated with 100 ng/ml was also included. T cell expansion over the course of 14 days was measured and the fold change in T cells expansion is shown in Figure 28A. CD3/CD28 dynabeads plus IL2 with or without IL12 had the most profound impact on T cell expansion followed by the T cells treated with soluble CD3/CD28 plus IL2 with or without IL12. Unstimulated cells and cell treated with soluble CD3/CD28 cells that did receive IL2 treatment were unable to expand over the course of the experiment. These results show that IL2 is required for T cell expansion, but IL12 may be dispensable.

[00630] The effect of IL12 on T cell activation was measured by determining the frequency of IFNgamma positive CD4+ and CD8 + T cells. IFNg is produced by activated T cells. Three different stimulation protocols were used. In the first protocol, cells were stimulated with

CD3/CD28 dynabeads for 2 days, following which the beads were washed off and the cells were treated with varying concentrations of IL12 for 7 days (from day 2 to day 9). At day 9, cells were restimulated with soluble CD3/CD28 and the frequency of IFNgamma positive cells was determined by FACS. The results are presented in Figure 28B as the percentage of cells. In the second protocol, following 2 day CD3/CD28 dynabeads stimulation, T cells were maintained in culture for a longer duration of 14 days i.e. from day 2 to day 16. At day 16 cells, were restimulated with soluble CD3/CD28. At day 16, the frequency of IFNgamma positive cells was measured. The results are presented in Figure 28C as the percentage of cells. In the third protocol, T cells were initially stimulated for 2 days with CD3/CD28 dynabeads and IL2, followed by treatment with IL2 only for 9 days (i.e. from day 2 to day 11), followed by IL12 treatment for 2 to 5 days. In the last two days of the experiment, cells were also restimulated with soluble CD3/CD28. IFNgamma positive CD4 and CD8 cells were measured using FACS. The third protocol mimics the environment that is presented to T cells in adoptive cell therapy, both during in vitro transduction and T cells expansion as well as the in vivo. The results are presented in Figure 28D as the percentage of cells. In both 7-day treatment with IL12 as well as 14-day treatment with IL12, shown in Figure 28B and Figure 28C respectively, restimulation with CD3/CD28 cells at the end of the experiment increased the percentage of IFNgamma positive cells. A half maximum effective concentration (EC50) of IL12 observed with the first protocol for CD8 cells was 50 pg/ml. The EC50 of IL12 observed with the second protocol was 12 pg/ml for CD4 cells and 65 pg/ml for CD8 cells. Long-term culture with CD3/CD28 further increased the dependence on re-stimulation and IL12 for IFNg production.

[00631] The results obtained with the third stimulation protocol are presented in Figure 28D. Immune cells treated with IL12 for the final 5 days of the experiment combined with CD3/CD28 restimulation showed the highest percentage of IFN gamma positive cells (EC50 = 24 pg/ml for CD4 cells and 40 pg/ml for CD8 cells), followed by cells that received IL12 for 2 days. Thus, T cells expanded in vitro can later differentiate in response to IL12, but restimulation may be required for IFNg production.

[00632] Taken together these results indicate that IL12 can stimulate IFN production in T cells when restimulated with CD3/CD28.

Example 24. Promoter selection for expression of SREs in T cells

[00633] The expression of SREs in a vector can be driven by either the retroviral long terminal repeat (LTR) or by cellular or viral promoters located upstream of the SRE. The activity of the promoter may vary with the cell type and thus promoter selection must be optimized for each

cell type. To identify optimal promoters, AcGFP (SEQ ID NO. 870) was cloned into pLVX. IRES Puro construct with a CMV or an EF1a promoter. Patient derived T cells and Sup T1 cells were transduced with the constructs and GFP expression was measured at day 3 and day 5 after transduction using FACS. As shown in Figure 29, both the CMV promoter and the EF1a can drive the expression of GFP in SupT1 cells and T cells. The percentage of GFP positive T cells was higher when GFP expression was driven by CMV promoter compared to an EF1a promoter, both at 3 days and 6 days after transduction. In contrast, the percentage of GFP positive cells was much higher when GFP expression was driven by the EF1a promoter when compared to the CMV promoter. Thus, the optimum promoter suitable for expression differs based on the cell type.

Example 25. Effect of ligand on T cell proliferation

[00634] The effect of ligands specific to the SREs of the invention on immune cell proliferation was measured to identify concentrations of the ligand that did not inhibit T cell growth or survival. T cells derived from two different donors were stimulated with CD3/CD28 and treated with ligand TMP at doses ranging from 0.04 μM to 160 μM or DMSO. The percentage of divided cells within the CD4 and the CD8 populations of T cells was measured using FACS. Concentrations of TMP ranging from 0.04 μM to 40 μM showed no effect on the percentage of divided cells within the CD8 and CD4 populations, while 160 μM concentration of TMP resulted in an 70-90% reduction in the percentage of divided cells. Thus, the optimal concentration of TMP for T cell based experiments was determined to be less than 160 μM.

Example 26. Effect of DD regulated CD19 CAR on tonic signaling

[00635] Chronic antigen activation can result in T cell exhaustion. To test if DD regulated CD19 CAR constructs induce tonic signaling, irradiated K562 cells expressing CD19 are plated into culture plates 12 hours before the addition of T cells expressing DD regulated CD19 CAR constructs with Interleukin 2. Cells are counted every two days and media is replaced. For repeated stimulations, cells are transferred to a new plate with K562-CD19 cells after 24 hours (for two stimulations) or every 12 hours (for four stimulations). For each condition, T cells are counted and analyzed by FACS for CAR, phenotypic and exhaustion markers every 12 hours. DD regulated constructs were analyzed in the presence or absence of ligand. Markers analyzed include CD25 and CD69 for activation status; CD62 and CD45RA for memory status; and exhaustion markers PD1, TIM3 and LAG3. DD regulated CD19 CAR constructs are expected to induce a lower percentage of cells that are positive for all three exhaustion markers- i.e.PD1,

TIM3 and LAG3 and a higher percentage of cells that are CD45A+/CD62L+ indicating less differentiated T cells. Constitutively expressed CD19CAR constructs may induce the expression of all three exhaustion markers and may have a more differentiated phenotype with a higher proportion of CD45-/CD62L- and CD45+/CD62L- cells.

Example 27. Functional analysis of DD regulated CD19 CAR

[00636] To test the ability of DD regulated CD19 CAR cells to kill target cells, primary T cell populations transduced with DD regulated CD19 CAR constructs are co cultured with K562 cells expressing CD19 (target cells) at a ratio of 5:1 in the presence or absence of the ligand specific to the DD e.g. Shield-1, TMP or MTX. Additional control combinations of T cells and target cells are also set up. These include DD regulated CAR expressing T cells co cultured with K562 cells (in the presence or absence of the ligand), T cells co cultured with K562 cells expressing CD19 and K562 cells expressing CD19 without T cell co culture. The K562 cells are fluorescently labelled with NucLight Red and co cultured with T cells for 30 hours. Cell death is monitored by labelling cells with Annexin V and the cell death in target K562 cells is monitored by evaluating cells that are positive for both Annexin V and NucLight Red. The ratio of Annexin V staining per target cell area is calculated. DD-CD19CAR expressing T cells are expected to be effective in killing target K562 cells expressing CD19 only in the presence of the ligand specific to the DD. Minimal target cell death is expected to occur when untransduced T cells are cocultured with CD19 expressing target cells; and with DD-CAR T cells (with or without ligand treatment) plus K562 cells (without CD19 expression).

Example 28. Generation of CD19 scFvs using the large phage antibody libraries

Construction of Primary Phagemid Library

[00637] Total RNA is prepared from 40 different samples of human peripheral blood lymphocytes and cDNA is synthesized using random primers. IgM variable regions are amplified using an IgM 3' primer and 5'VH primers. Pooled primers are also used to amplify the Vk and VL. An additional PCR step is added to include restriction sites as well as to introduce a region of overlap containing an scFv loxP linker. scFvs are obtained by mixing equimolar amounts of VH and VL genes and performing assembly. The scFvs are then cloned into pDAN5 vectors to obtain a primary library of approximately 10^8.

Recombination and secondary of the secondary library

[00638] To induce recombination, bacterial strain BS1365 (which express Cre-recombinases constitutively) are infected with primary phagemid library at an MOI of 20:1. This results in

bacteria containing multiple phagemids, each of which encodes different VH and VL genes, which can be recombined by the Cre recombinase. Since the phagemid arise from bacteria containing many different scFv, the phenotype and genotype are not coupled. Phagemids derived from the bacteria are used to infect bacteria that do not express Cre (e.g. DH5a) at a low MOI of ≤ 0.1 to couple genotype to phenotype.

CD9 expression constructs and cell lines

[00639] Human CD19 isoforms described in Table 14 are cloned into appropriate vectors and transfected into cell lines with low endogenous CD19 expression such as K562 and 3T3 cell lines. The CD19 expressing lines i.e. K562- CD19 or 3T3 -CD19 cells, are used for positive selection of scFvs in the phage display library. The parental K562 and 3T3 are used for the negative selection.

Selection of antibodies recognizing CD19 on cell surface

[00640] The secondary phage display library is pre-cleared by screening with parental cells to remove non-specific binding phages. The precleared phages are incubated with K562-CD19 or 3T3-CD19 cells, and bound phages are recovered and amplified for next round of selection. Three rounds of selection are performed to enrich for CD19 binders. FMC63-distinct scFvs i.e. scFvs that bind to epitopes distinct from FMC63, are selected in a parallel selection process by blocking the FMC63 epitope with an excess of FMC63 antibody.

[00641] The affinity of the scFv to CD19 is a critical aspect that determines the performance of the antibody in pharmacokinetic and immune response assays. Affinity measurements for 96 scFv clones are made using techniques such as ELISA and surface plasma resonance which provide on-rate (Ka), off-rate (Kd), and affinity constant (KD).

[00642] scFv clones with desired off rates are subjected to Sanger sequencing to identify unique clones that bind to CD19 expressing cells but not parental cells. Identified clones are then subject to epitope binning, using a competitive immunoassay that is used to characterize and then sort a library of scFvs against a target protein, e.g. CD19. scFvs against CD19 are tested against all other CD19 scFvs identified from the library, in a pairwise fashion to identify scFvs that prevent the binding of other scFvs to an epitope of CD19 antigen. After a profile is created for each CD19 scFv, a competitive blocking profile is created for each scFv relative to the others. Closely related binning profiles indicate that the antibodies have the same or a closely related epitope are binned together.

[00643] scFvs obtained at each of step of the selection process are subject to deep sequencing methods such as Ion Torrent/MiSeq. Heavy chain CDR3 sequences, including those that do not

bind to FMC63 are identified using the Abmining ToolBox (D'Angelo S et al. (2014) MAbs. 6(1): 160–172) and top ranking HCDR3s are identified. HCDR3 specific primers designed from the DNA sequence of the top ranked sequences are then used to amplify scFv clones by inverse PCR and the PCR product is cloned into expression vectors.

Example 29. CD19 scFv affinity

[00644] The affinity of the scFv to the CD19 antigen is a critical aspect that determines the performance of the antibody in pharmacokinetic and immune response assays. Affinity measurements are made using techniques such as ELISA and surface plasma resonance which provide on-rate (Ka), off-rate (Kd), and affinity constant (KD).

[00645] Antibodies with varying affinities are identified using cells that have high or low ectopic expression of CD19. K562-CD19 cells and parental K562 cells with low CD19 expression are sorted by FACS using CD19 antibodies e.g. FMC63 to determine surface expression of CD19. Cells are sorted into bottom 5% (i.e. low CD19 expressing cells), top 5% (high CD19 expressing cells) and the rest of the population of cells is categorized as median CD19 expressing cells.

Example 30. Screening strategy for identifying FMC63-distinct CD19 scFvs

CD19/Fc fusion proteins

[00646] FMC63 binds to human CD19 in the region encoded by exon 2. To identify FMC63-distinct CD19 scFvs, human CD19 (Exon 1-4) or human CD19 (Exon 1,3,4) are fused with IgG to generate CD19-IgG fusion proteins, CD19sIgG1-4 and CD19sIgG1,3,4 respectively. CD19-IgG fusion proteins are used for antibody screening. 96-well plates are coated with capture antibodies and incubated with CD19sIgG1-4 or CD19sIgG1,3,4 fusion protein. The plates are washed and incubated with candidate CD19 scFvs identified in Example 28. The plates are washed again and incubated again with reporter (e.g. Alkaline phosphatase) conjugated detection antibodies and detected using reporter compatible detection methods. Capture antibodies may be antihuman IgG Fc antibodies, or the FMC63 antibody (as a control). The detection antibody may be anti-human IgM antibody. FMC63-distinct CD19 scFvs are expected to bind to (CD19sIgG1,3,4) and (CD19sIgG1-4). In contrast, candidate CD19 scFvs that bind to epitopes that are identical or overlap with FMC63's epitope are expected to only bind to (CD19sIgG1-4).

Competition assay

[00647] CD19 expressing K562 cells are incubated with nano molar concentrations of tagged candidate CD19 scFvs e.g. identified in Example 28 and fixed concentration of tagged FMC63

scFv for competition binding assays. Cells are washed and stained with the secondary antibody corresponding to the tag used in the candidate CD19 scFv. Mean fluorescence intensity is measured using flow cytometry. As a negative control, CD19 K562 expressing cells are incubated with varying concentrations of tagged candidate CD19 scFv alone or FMC63 alone. For FMC63-distinct CD19 scFvs, it is expected that there will be no competition for binding to CD19 between the candidate CD19 scFvs and FMC63. Thus, the mean fluorescence intensity of the tagged candidate CD19 scFv is expected to increase with increasing concentrations of the candidate CD19 scFv, while the mean fluorescence intensity of tagged FMC63 antibody is not expected to decrease with increasing concentrations of the candidate CD19 scFv. This would indicate that the FMC63 is not displaced from its epitope by the addition of the candidate CD19 scFv, suggesting distinct binding epitopes. For candidate CD19 scFv that bind to the same epitope as FMC63, a decrease in the fluorescence intensity of FMC63 with increasing concentrations of the candidate CD19 scFv is expected.

Example 31. Functional analysis of FMC63-distinct CD19 CAR constructs

[00648] FMC63-distinct CD19 scFvs engineered to generate FMC63-distinct CD19 CAR constructs with destabilizing domains, linkers, transmembrane and intracellular domains described in Table 1, and Tables 6, 7, 8A or 8B. The ability of FMC63-distinct CD19 CAR to induce cell activation, cytotoxicity and proliferation is compared to the FMC63-CD19 based CAR constructs in Jurkat cells. Constructs are also analyzed for their ability to induce the upregulation of exhaustion markers, PD1, TIM3 and LAG3, and constructs that are positive for multiple exhaustion markers are excluded from the analysis. Constructs that can induce Jurkat cell activation and cytotoxicity but not exhaustion markers are transduced into T cells and their efficacy is compared with the constitutively expressed FMC63-based CD19 CAR construct. It is expected that DD regulated FMC63-distinct CD19 CAR constructs will demonstrate superior cytotoxic capabilities with minimal tonic signaling as compared to FMC63 CD19 CAR constructs.

Example 32. Ligand dependent target cell death induced by DD regulated CD19 CAR

[00649] To test the antigen specificity of cell killing by T cells engineered to express constitutive or DD-containing CAR construct, CD19 was ectopically expressed in the antigen negative K562 cell line. CD19 expression was measured using anti-CD19 antibody conjugated to Phycoerythrin (PE). Figure 30A shows the expression of CD19 in parental K562 cells and K562-CD19 cells, wherein CD19 is ectopically expressed.

[00650] To test the ability of DD regulated CD19 CAR cells to kill target cells, primary T cell populations were transduced with DD regulated CD19 CAR constructs, OT-CD19-024 with human DHFR DD and an EF1a promoter. Transduced T cells were co cultured with K562 cells expressing CD19 (target cells) at a ratio of 5:1 in the presence or absence of TMP (100μM). Additional control combinations of T cells and target cells were also set up. These included DD regulated CAR expressing T cells co cultured with antigen-negative K562 cells (in the presence or absence of the ligand), untransduced T cells co cultured with K562 cells expressing CD19 and K562 cells expressing CD19 without T cell co culture. The T cells utilized for this experiment were transduced with the OT-CD19-024 construct (or untransduced) and expanded for 11 days using protocols described in previous examples, frozen, thawed and co-cultured with target cells. Target cells were treated with Mitomycin C to prevent their proliferation. The K562 or K562-CD19 target cells stably expressing the fluorescent protein NucLight Red were co cultured with T cells for 300 hours. Cell death was monitored by labelling cells with Annexin V and the cell death in target K562 and K562-CD19 cells was monitored by evaluating cells that were positive for both Annexin V and NucLight Red using the IncuCyte® Live Cell Analysis System (Essen Biosciences, Ann Arbor, MI). The results are presented in Figure 30B, where the killed target cells represented on the y axis are based on target cells that are positive for both NucLight Red and Annexin V. Figure 30C, shows the killed target size as measured in (μM/well) at day 5. Target cell killing was observed with the OT-CD19-024 construct only in TMP treated co-cultures of T cells and K562 target cells ectopically expressing CD19. No cell killing was observed in untreated controls of the same co-culture set up and when T cells were co cultured with parental K562 cells that do not express CD19 in the presence or absence of ligand. These data show that regulated CARs display ligand- and target-dependent cell killing with minimal basal off-state.

Example 33. *In vitro* CAR-T cell functional analysis

[00651] The efficacy of T cells expressing DD regulated CD19 CAR constructs in functionally interacting with target cells is evaluated. To interact with the CD19CAR T cells, the chosen target cells express CD19 naturally or ectopically. In this context, target cells which have high endogenous expression of CD19 such as Nalm6, Raji, Reh, Sem, Kopn8, and Daudi cells. Alternatively, target cell lines may be engineered by ectopic expression of CD19 in cell lines that have low endogenous expression of CD19 such as K562. Multiple assays are used to measure functionality. Prior to co culture, the target cells are optionally cultured in the presence of presence of mitomycin C to prevent target cell proliferation. This ensures that target cell growth

does not out compete T cell growth. Cytotoxicity assays are used to measure the ability of T cells induce target cell death. Target cells are engineered to express Renilla or Firefly luciferase and co cultured with T cells expressing DD regulated CD19 CAR constructs for 18 to 24 hours in the presence of the ligand related to the DD or vehicle control. At the end of co culture, cells are lysed and luciferase activity is measured using appropriate substrate. Luciferase activity is expected to increase when DD regulated CD19 CAR expressing T cells are co cultured with CD19 expressing target cells in the presence of ligand. Cytotoxicity is not expected in vehicle control cells or when the target cells do not express CD19 are utilized.

[00652] Engagement of the CD19 CAR with CD19 antigen results in the activation of T cells which is measured 24 hours after co culture of CAR expressing T cells and target cells. Activation of T cells is evaluated by measuring levels of IFNg, IL2, and CD69. T cell proliferation in response to antigen mediated T cell activation is measured by labelling T cells with Carboxyfluorescein succinimidyl ester, which is used to trace cells across multiple generations. Labelled T cells are cultured with Mitomycin treated target cells and cell proliferation is tracked over a period of 3 to 5 days. T cell proliferation and activation is expected to increase when DD regulated CD19 CAR expressing T cells are co cultured with CD19 expressing target cells in the presence of ligand. Both parameters are not expected in vehicle control cells or when the target cells do not express CD19 are utilized.

[00653] Activation of T cells results in degranulation, an exocytic process by which cytotoxic T cells release molecules like perforin and granzymes which enable target cell killing. Degranulation is measured by analysis of media for indications of exocytosis e.g. CD107 by FACS and by markers of degranulation such as perforin and granzyme using immunoassays.

Example 34. Ligand dependent target cell death induced by DD regulated CD19 CAR

[00654] To test the ability of DD regulated CD19 CAR cells to kill target cells, primary T cell populations are transduced with DD regulated CD19 CAR constructs are co cultured with K562 cells expressing CD19 (target cells) at a ratio of 5:1 in the presence or absence of the ligand specific to the DD e.g. Shield-1 (1μM), TMP (100μM) or MTX. Constructs with FKBP, ecDHFR or human DHFR DDs may be utilized. Constructs with either CMV, EF1a or PGK promoters may also be used. Multiple combinations of T cells and target cells are set up. These included DD regulated CAR expressing T cells co cultured with K562 cells (in the presence or absence of the ligand), T cells co cultured with K562 cells expressing CD19 and K562 cells expressing CD19 without T cell co culture. Additional controls include target cells only; untransduced T cells; T cells transduced with empty vector. The T cells utilized for this

experiment are expanded for 11 days using protocols described in previous examples, frozen, thawed and transduced with the CD19 CAR constructs. Target cells are treated with Mitomycin C to prevent their proliferation. The K562 cells are fluorescently labelled with NucLight Red and co cultured with T cells for 300 hours. Cell death is monitored by labelling cells with Annexin V and the cell death in target K562 cells is monitored by evaluating cells that are positive for both Annexin V and NucLight Red using the IncuCyte® Live Cell Analysis System (Essen Biosciences, Ann Arbor, MI). Target cell killing is expected with the DD regulated CAR constructs only in the presence of ligand and when K562 target cells ectopically expressing CD19 are utilized. No cell killing is expected in untreated controls of the same co-culture set up and when T cells are co cultured with parental K562 cells that do not express CD19 in the presence or absence of ligand. Constitutive constructs are predicted to show cell killing both in the presence of ligand. Cell killing is also not expected in cocultures with untransduced T cells, T cells transduced with empty vector; and cultures of target cells only.

Example 35. Effect of Ligand on Cytokine Expression

[00655] To study the effect of ligand on the expression of cytokines in regulated CD19 CAR constructs, T cell populations were transduced with empty vector, OT-CD19-017, OT-CD19-023, OT-CD19-024, or OT-CD19-025. $5x10^4$ transduced T cells were co cultured for 48 hours at an E:T (effector to target cell) ratio of 5:1 in the presence or absence of TMP or Shield-1. Target cells were treated with 50 ug/ml of Mitomycin C to prevent their proliferation. The cytokine concentration of IFNγ and IL2 in the media supernatant were determined for each construct using MSD V-PLEX Proinflammatory Panel 1 Human Kit. The readout was obtained using a MESO QuickPlex SQ120. As shown in Figure 31A, a 6 fold increase in IFNγ concentration was seen with the addition of ligand for OT-CD19-024, and a 2 fold increase in IFNγ concentration was seen with the addition of ligand for OT-CD19-025. As shown in Figure 31B, a 6 fold increase in IL2 was seen for OT-CD19-024 with the addition of ligand and a 9 fold increase was seen for OT-CD19-025 with TMP.

Example 36. *In vivo* time course study of IL12 levels in mice

[00656] HCT116 parental cells or cells transduced with IL12 constructs (OT-IL12-020, OT-IL12-026, or OT-IL12-029) were injected into immune compromised CD1 nude mice (n=4 per group) according to the study design in Table 30 below.

Table 30. Study Design

HCT116 cells	Day 15 Dose	Concentration	Route of Day 15 Dose
OT-IL12-026	Vehicle	n/a	Intraperitoneal
	Shield-1 (1x)	10 mg/kg	Intraperitoneal
	Shield-1 (3x, 2h apart)	10 mg/kg	Intraperitoneal
OT-IL12-029	Vehicle	n/a	Intraperitoneal
	Shield-1 (1x)	10 mg/kg	Intraperitoneal
	Shield-1 (3x, 2h apart)	10 mg/kg	Intraperitoneal
OT-IL12-020	Vehicle	n/a	Intraperitoneal
	Shield-1 (1x)	10 mg/kg	Intraperitoneal
Parental	Vehicle	n/a	Intraperitoneal
	Shield-1 (1x)	10 mg/kg	Intraperitoneal

[00657] The mice were bled (blood harvested for plasma PK and IL12 MSD) at day 14 after subcutaneous injection of $5x10^6$ cells (day 0), and 6, 10, and 24 hours post the day 15 dosing. At the end of the study, tumor and kidneys were minced with the razor in 500 ul PBS, spun down, and supernatant isolated for IL12 Meso Scale Diagnostic(MSD) assay.

[00658] As shown in Figure 32A, the basal plasma IL12 levels of the DD constructs were high, but the OT-IL12-026 and OT-IL12-029 constructs were still 100-fold lower than the constitutive (OT-IL12-020) construct. When Figure 32A is shown as fold change from pre-dose plasma, OT-IL12-026 shows regulation at 6 and 10 hours. Figures 32B and 32C show that IL12 is detectable in kidney (Figure 32B) and tumor (Figure 32C) and the levels coordinate with plasma levels.

Example 37. *In vivo* time course study of IL12 levels in mice

[00659] HCT116 parental cells or cells transduced with IL12 constructs (OT-IL12-020, OT-IL12-026) were injected subcutaneously into Matrigel plus in female NSG mice (implant 200 ul matrigel plug with $1x10^7$ cells) (n=4) according to the study design in Table 31 below.

Table 31. Study Design

HCT116 cells	Dose	Harvest Plug	Coverage above EC50
OT-IL12-026	Vehicle (1x)	8 hours after 1st dose	-
	Vehicle (1x)	24 hours after 1st dose	-
	AquaShield-100 mg/kg (1x)	8 hours after 1st dose	4 hours
	AquaShield-100 mg/kg (2x, 4 hours between doses)	8 hours after 1st dose	8 hours
	AquaShield-100 mg/kg (1x)	24 hours after 1st dose	4 hours
	AquaShield-100 mg/kg (2x, 4 hours between doses)	24 hours after 1st dose	8 hours
	AquaShield-100 mg/kg (3x, 4 hours between doses)	24 hours after 1st dose	12 hours
OT-IL12-020	Vehicle (1x)	24 hours after 1st dose	-
Parental	Vehicle (1x)	24 hours after 1st dose	-

[00660] Terminal collection of plasma (for IL12 MSD), plug supernatants and kidneys were collected. As shown in Figure 33A, regulation of IL12 was achieved *in vivo* with high dose Aquashield. There was less regulation observed in the plasma (Figure 33B) and there was some flexi-IL12 detected in the kidneys (Figure 33C).

Example 38. Shield-1 Can Induce ~40-50x Increases in IL12 Production by Primary Human T Cells Transduced with the IL12-026 Construct

[00661] On Day 0, primary human T cells were stimulated with Dynabeads (T-expander CD3/CD28) at a 3:1 bead:cell ratio. The next day, lentiviruses (empty vector (pLVX-EF1a-IRES-Puro), OT-IL12-020 (constitutive), or OT-IL12-026 (regulated)) were added at a multiplicity of infection (MOI) of 10 in the presence of LentiBOOST and 5% FBS. On day 2, the cells were washed to remove the LentiBOOST and the bead:cell ratio was reduced to 1:3, and fresh 10% media and IL2 were added. On days 6, 9, and 13 the cells were counted for equal cell number plating, media replaced, ligand was added, and cells were either left unstimulated or restimulated with soluble ImmunoCult™ Human CD3/CD28 T Cell Activator (StemCell Technologies). After overnight incubation (on days 7, 10, and 14), the supernatants were collected for IL12p40 and p70 MSD assay, and transduction efficiency was analyzed by FACS. OT-IL12-026 T cells were found to be 7% transduced, and OT-IL12-020 (constitutive) T cells were 13% transduced on day 7. Restimulation was shown to increase the expression of IL12 (Figure 34A). Ligand increased production of IL12 by 10-day expanded OT-IL12-026 expressing T cells by 40-50 fold (Figure 34B and Figure 34C).

Example 39. Dose Response of Shield-1 on Transduced T Cells

[00662] Human T cells were activated with CD3/CD28 Dynabeads (Life Technologies) for 1 day prior to transduction with lentiviruses (OT-IL12-026 or vector control), followed by 12-13 days of expansion in culture. T cells that had been transduced with different amounts of virus (4-40 MOI) were exposed to either a dose response of Shield-1 for 24h (left panel). T cells that had been transduced at an MOI of 14 were treated with 1uM Shield-1 or vehicle control for increasing amounts of time (right panel). The levels of IL12 that had accumulated in the supernatants (from 100,000 cells per 200uL media) were measured using human IL12p40 MSD V-plex assay kits (Meso Scale Discovery).

[00663] From the analysis, it was shown that the increase in IL12 production by T cells expressing OT-IL12-026 is dose responsive to the ligand, Shield-1 Figure 35A, and accumulates over time Figure 35B.

Example 40. *In Vivo* Dose Response, and Repeat Dosing of AquaShield in NSG Mice with Transferred T Cells Expressing OT-IL12-026

[00664] Primary human T cells were stimulated with Dynabeads (T-expander CD3/CD28) at a 3:1 bead:cell ratio. The next day, lentiviruses (OT-IL12-020 (constitutive), OT-IL12-026 (regulated), or vector control) were added at a multiplicity of infection (MOI) of 10 in the presence of LentiBOOST and 5% FBS. The following day, T cells were washed to remove the LentiBOOST and the bead:cell ratio was reduced to 1:3, and fresh 10% media and IL2 were added. The T cells were expanded for a total of 10 days, and then $25x10^6$ vector control or OT-IL12-026 transduced T cells or $10x10^6$ constitutive OT-IL12-020 transduced T cells were transferred into NSG mice (study day 0). Three days after cell transfer, the animals were dosed with either vehicle or AquaShield (10, 50 or 100mg/kg). Blood was sampled for plasma analysis of IL12p70 by MSD assay at 0, 4, 8, and 24h post dosing (Figure 36A). Clear dose responsive increases in plasma IL12 was observed.

[00665] On day 5 post T cell transfer, animals were dosed a second time with AquaShield (Figure 36B). A second increase in plasma IL12 was observed upon repeat dosing with AquaShield.

Example 41. *In Vivo* Regulation of DD-12 Expressed in T Cells

[00666] To determine whether ligand can stabilize DD-IL12 *in vivo* upon sequential dosing of AquaShield, T cells are transduced with DD-IL12-expressing constructs (OT-IL12-020 or OT-IL12-026) and implanted into mice (n=4 per group) (day 0) as outlined in the study design below.

Table 32. Study Design

Group	Description
A	Empty Vector, Day 3-6: oral vehicle daily for 4 days
B	OT-IL12-020, Day 3-6: oral vehicle daily for 4 days
C	OT-IL12-026: Day 3-6: oral vehicle daily for 4 days
D	OT-IL12-026, Day 3-6: Aquashield 50 mg/kg orally daily for 4 days
E	OT-IL12-026, Day 4 and 6: Aquashield 50 mg/kg orally
F	Empty Vector, Day 5 and 10: oral vehicle
G	OT-IL12-020, Day 5 and 10: oral vehicle
H	OT-IL12-026, Day 5 and 10: oral vehicle
I	OT-IL12-026, Day 5 and 10: Aquashield 50 mg/kg orally
J	OT-IL12-026, Day 10: Aquashield 50 mg/kg orally

[00667] For each group, a pre-bleed sample is collected as well as samples at 4 hours and 24 hours after each dose. At the end of the study, tissue and organ samples are collected. FACS analysis is conducted to determine cell numbers and Th1 markers.

[00668] On Day 0, primary human T cells were stimulated with Dynabeads (T-expander CD3/CD28) at a 3:1 bead:cell ratio. The next day, lentiviruses (empty vector (pLVX-EF1a-IRES-Puro), OT-IL12-020 (constitutive), or OT-IL12-026 (regulated)) were added at a multiplicity of infection (MOI) of 10 in the presence of LentiBOOST and 5% FBS. On day 2, the cells were washed to remove the LentiBOOST and the bead:cell ratio was reduced to 1:3, and fresh 10% media and IL2 were added.

[00669] In vitro evaluation of these cells is shown under Figure 37A-37C.

[00670] After 10 days of expansion, T cells were injected into NSG mice (12×10^6 cells injected, cells were 15% (constitutive) and 7.5% (regulated) IL12 positive by FACS). For each group, a pre-bleed sample was collected as well as plasma samples at 4 hours and 24 hours after each dose. At the end of the study, tissue and organ samples are collected. FACS analysis was conducted to determine T cell numbers in the blood and to assess Th1 phenotypic markers.

[00671] As shown in Figure 37A, IL12 expression in response to sequential pulsed doses of ligand (50 mg/kg Aquashield administered orally on day 4 and 6 (50 mpk Aquashield q48hr)) was elevated in the plasma of mice with T cells expressing OT-IL12-026 as compared to the vehicle treated controls. T cells expressing the empty vector control did not produce IL12. T cells transduced with OT-IL12-020 (IL12-020), the constitutive control, produced IL12 throughout the time course.

[00672] In Figure 37B, elevated plasma IL12 expression in response to sequential pulsed doses of ligand (50 mg/kg Aquashield administered orally for 4 days (day 3-6) (50 mpk Aquashield QDx4)) was seen in mice bearing OT-IL12-026 expressing T cells as compared to the vehicle treated controls. Cells transduced with OT-IL12-020 (IL12-020), the constitutive control, produced IL12 throughout the time course.

[00673] Figure 37C shows the IL12 expression over 11 days for the constitutive construct OT-IL12-020 (IL12-020). Ligand-regulated expression of IL12 from T cells expressing DD-IL12 from the construct OT-IL12-026 was seen in mice treated with 50 mg/kg Aquashield administered orally on day 5 and 10 (50 mpk Aquashield d5/10). T cells expressing the empty vector control did not produce IL12.

[00674] Figure 37D shows ligand-induced regulation of plasma IL12 expression from T cells expressing DD-IL12 from the construct OT-IL12-026 when mice were treated orally with 50 mg/kg Aquashield on day 10 (50 mpk Aquashield d10). The single ligand pulse increased plasma IL12 levels over those detected in vehicle-treated control mice harboring OT-IL12-026 expressing T cells.

[00675] Regulation of IL12 for all constructs shown in Figures 37A-37D did not impact IFNγ levels, instead the levels of IFNγ gradually rose over time. This is likely due to the exposure of the T cells to IL12 in culture during the *in vitro* expansion phase. However, ligand-induced regulation of IL12 increased granzyme B (GrB) (Figure 37E) and perforin expression (Figure 29F) by CD8+ T cells *in vivo* at day 7 post *in vivo* T cell transfer.

Example 42. Effect of PGK Promoter and N-terminal FKBP

[00676] HEK293T cells were transiently transfected with Lipofectamine 3000 and 2ug plasmid DNA each of: OT-IL12-019 (PGK promoter), OT-IL12-020 (EF1alpha promoter), OT-IL12-025 (PGK promoter, C-terminal FKBP domain), OT-IL12-026 (EF1alpha promoter, C-terminal FKBP domain), OT-IL12-046 (N-terminal FKBP). Ligand (1uM Shield-1) was added one day after transfection, and the cells were further cultured for 2 more days. IL12 secretion into the supernatants was quantitated by IL12p40 MSD assay. Genomic DNA (gDNA) and messenger RNA (mRNA) was purified from the cells. The levels of construct DNA integration into the cellular genome and levels of IL12 mRNA expression were quantitated by qPCR using primers specific to the WPRE element and IL12 within the respective constructs.

[00677] The gDNA qPCR analysis demonstrated that the FKBP DD-containing constructs had integrated to similar levels within the cellular genomes, and that the PGK promoter, as expected, generated less IL12 mRNA expression than the EF1alpha promoter (Figure 38A).

[00678] Due to the lower levels of mRNA transcription induced by the PGK promoter, the IL12p40 MSD assay also demonstrated that the PGK promoter reduced both basal and peak IL12 levels of secretion as compared to the construct using the EF1alpha promoter. The lower basal levels of IL12 production downstream of the PGK promoter resulted in ~2 fold improved ligand-induced IL12 regulation as compared with the construct with the EF1alpha promoter (Figure 38B). More specifically, the ligand-induced regulation of IL12 expression increased from 6-fold to 13-fold with the change from the EF1alpha to the PGK promoter, respectively.

[00679] Constructs containing FKBP either at the N-terminus or at the C-terminus of IL12 were integrated similarly into the cellular genome and generated similar levels of mRNA (Figure 38A). However, while C-terminal containing FKBP constructs regulate IL12 expression, the N-terminal-containing FKBP construct failed to regulate IL12 expression (Figure 38B).

Example 43. Kinetics of ligand-dependent stabilization of DD-IL15- IL15Ra

[00680] The on/off kinetics of ligand-dependent stabilization of DD-IL15-IL15Ra was measured in CD4 positive T cells. T cells were activated with CD3/CD28 beads at 3:1 bead to T cell ratio in 24-well plates for 24 hrs. Lentivirus was added to wells in the presence of

LentiBoost reagent, and cells were incubated for another 24 hrs and washed. Cells were resuspended in fresh media, and media was added every 2-3 days to expand and maintain cells at 0.5-1x10^6/ml. After 7 days of expansion, T cells transduced with the ecDHFR DD-IL15-IL15Ra fusion construct (OT-IL15-009) were treated with 100μM ecDHFR ligand Trimethoprim (TMP) or vehicle control, DMSO. At multiple time points (i.e., 1, 2, 4, 6, 8, 15, 22 and 24 hrs) after TMP treatment, the transduced T cells were collected and analyzed for IL15Ra surface expression using anti-IL15Ra antibodies by flow cytometry. Untransduced T cells were used as a negative control. The T cells were sorted into CD4 positive and CD8 positive populations and the percentage of IL15Ra positive CD4 positive T cells was analyzed. Figure 39 shows the kinetics of surface expression of IL15Ra on CD4 T cells after TMP treatment. Among the CD4 positive T cells transduced with the OT-IL15-009 construct, the proportion of cells with surface expression of IL15Ra remained similar for both TMP treated and DMSO treated cells until 2 hrs after TMP treatment, and was comparable to that of untransduced cells. However, from 4 hrs after TMP treatment, the cells transduced with the OT-IL15-009 construct and treated with TMP exhibited an increased proportion of cells with surface expression of IL15Ra. This trend was observed until 22 hours after treatment with TMP. The CD4 positive T cells with surface-expressed IL15Ra cells constituted ~1% of untransduced cells, indicating that the proportion of cells that expressed endogenous IL15Ra is low.

Example 44. Ligand-dependent stabilization of DD-IL15-IL15Ra fusion molecules *in vivo*

[00681] To examine whether ligand treatment induces stabilization of the DD-IL15-IL15Ra fusion molecules *in vivo*, HCT116 cells transduced with the OT-IL15-009 construct were implanted subcutaneously in BALB/c nude mice and treated with TMP. TMP was orally administered to mice at a dose of 100 mg/kg, twice a day for 11 days after implantation, followed by administration of TMP at the dose of 300 mg/kg, twice a day for 6 days. As a negative control, separate mice implanted with HCT116 cells transduced with the OT-IL15-009 construct were treated with the vehicle twice a day for 17 days. At 4 hrs after the last dosing of TMP or the vehicle control, tumors were harvested from the mice and analyzed for the levels of IL15-IL15Ra fusion molecules by western blotting. As shown in Figure 40, HCT116 tumors harvested from mice treated with TMP exhibited elevated levels of IL15-IL15Ra expression, compared to tumors treated with the vehicle. The GAPDH level was analyzed as a loading control. These data show that administration of ligand enabled stabilization of the DD-IL15-IL15Ra fusion molecule *in vivo*.

[00682] Consistent with the efficacy of TMP-dependent IL15-IL15Ra stabilization *in vivo*, elevated levels of TMP (399.38 ng/g tumor) were observed in HCT116 tumors harvested from

mice treated with TMP for 17 days. The levels of TMP associated with HCT116 tumors were considerably higher than those observed in mouse plasma at day 3 (15.67 ng/ml plasma) and at day 17 (99.5 ng/ml plasma), indicating that the orally administered TMP was successfully delivered to and accumulated in HCT116 tumors implanted in mice.

Example 45. Shedding resistant IL15-IL15Ra constructs

[00683] To maintain the efficiency of the trans-presentation of IL15 via the IL15-IL15Ra fusion molecule, the IL15-IL15Ra shedding needs to be prevented. For this purpose, new DD-IL15-IL15Ra and constitutive IL15-IL15Ra constructs are designed through a variety of modifications on the IL15-IL15Ra fusion molecule. For example, the IL15 molecule or the IL15Ra molecule is truncated or mutated to remove presumable cleavage sites. IL15Ra has a cleavage site (PQGHSDTT from the position 168 to 175 of SEQ ID NO. 803) in the extracellular domain immediately distal to the transmembrane domain of the receptor, as described by Bergamaschi C *et al.* (2008). J Biol Chem ;283(7):4189-99; Anthony SM *et al.* (2015). PLoS One. 10(3): e0120274), and International Patent Application Publication Nos. WO2014066527 and WO2009002562 (the contents of each of which are incorporated herein by reference in their entirety). Tumor necrosis factor-alpha-converting enzyme (TACE/ADAM17) has been implicated as a protease that cleaves between glycine (at the position 170 of SEQ ID NO. 803) and histidine (at the position 171 of SEQ ID NO. 803) and generates a naturally occurring soluble form of IL15Ra. The same mechanism can be responsible for the IL15-IL15Ra shedding. Hence, the cleavage site of IL15Ra is mutated such that cleavage by an endogenous protease is prevented. The mutation of the cleavage site is introduced by substitution, insertion or deletion of amino acid residues. The IL15-IL15Ra fusion molecule is also modified such that the full-length or truncated IL15-IL15Ra fusion molecule is fused to heterologous hinge domains and/or heterologous transmembrane domains. As non-limiting examples, variants of IL15Ra can be utilized. Additionally, the length and sequence of the linkers that connect IL15 and IL15Ra are modified.

[00684] To confirm that the modifications on the IL15-IL15Ra fusion molecule prevent shedding, the new DD-IL15-IL15Ra or constitutive IL15-IL15Ra constructs are introduced into HCT-116 cells. Surface expression of IL15 and IL15Ra on the HCT-116 cells is examined by flow cytometry using anti-IL15 and IL15Ra antibodies to assess surface IL15-IL15Ra shedding. The presence or absence of IL15 in the cell culture supernatant is also analyzed by MSD assay. As a functional assay based on the sensitivity of NK cell activation by shed IL15 in tumor supernatant, the transwell assay is conducted using HCT-116 cells transduced with new DD-IL15-IL15Ra or constitutive IL15-IL15Ra expressing constructs and NK cells. The new DD-

IL15-IL15Ra-expressing constructs that do not induce activation of NK cells in the presence of ligand and the new constitutive IL15-IL15Ra-expressing constructs that do not induce activation of NK cells are chosen for use in future experiments.

Example 46. Regulated expression of IL15-IL15Ra fusion molecule with C-terminal DD

[00685] A fusion molecule is generated by fusing membrane bound IL15, IL15 Receptor alpha subunit (IL15Ra) and a human DHFR (DD). These fusion molecules were cloned into pLVX-EF1a-IRES-Puro vector.

[00686] To test ligand dependent IL15-IL15Ra production, 1 million HEK-293T cells were plated in a 6-well plate in growth media containing DMEM and 10 FBS and incubated overnight at 37°C, 5% CO2. Cells were then transfected with 100ng of constitutive IL15-IL15Ra (OT-IL15-008) or DD linked IL15-IL15Ra (OT-IL15-037 or OT-IL15-040) using Lipofectamine 2000 and incubated for 24 hrs. Following the incubation, media is exchanged for growth medium with or without 50μM Trimethoprim (TMP) and further incubated for 48 hrs. Cells were harvested and IL15 levels are analyzed via western blotting using human IL15 antibody (Abcam, Cambridge, UK). The molecular weight of IL15Ra in OT-IL15-037 and OT-IL15-040 appeared to be the same as OT-IL15-008.

[00687] To test if IL15 is shed into the media, supernatant from HEK293 cells expressing IL15-IL15Ra fusion constructs was subject to immunoassays such as MSD (Rockville, Maryland). 48 hours after transfection, cells were analyzed and, as expected, constitutive IL15-IL15Ra construct OT-IL15-008 showed high surface expression of IL15 in the presence and absence of ligand. OT-IL15-037 and OT-IL15-040 showed the ligand (Trimethoprim) dependent surface expression of IL15 and IL15Ra (Figure 41). The detection of membrane bound IL15-IL15Ra fusion constructs in the supernatant suggests that IL15 constructs are likely shed from the cell surface.

Example 47. Effect TMP exposure to TMP *in vitro* on membrane bound IL15 expression

[00688] In order to determine if the dose and time of exposure to TMP *in vitro* influenced membrane bound IL15 expression, an *in vitro* dose response study was conducted with T cells expressing OT-IL15-073.For this purpose, T cells were activated with CD3/CD28 beads at 3:1 bead to T cell ratio in 24-well plates for 24 hrs. Lentivirus was added to wells. After 24 hrs, fresh media was added every 2-3 days to expand cells while maintaining cells at 0.5-1x10^6/ml. On day 11 of expansion. T cells treated with TMP starting at 100 uM, 10x dilutions and 9 points were analyzed after 2 hours in culture (washed 3x after TMP addition, fresh media added without TMP for 22 hours), 6 hours in culture, or 24 hours in culture and the results are shown in Figure

42A. As shown in Figure 42B and Table 33, this study showed that TMP ligand regulates membrane bound IL15 expression and the dose and time of exposure to TMP *in vitro* influences membrane bound IL15 expression.

Table 33. Membrane Bound IL15 Expression

TMP Treatment	EC50, uM (%IL15+IL15Ra+)	EC90, uM (%IL15+IL15Ra+)	EC50, uM (total IL15 MFI)	EC90, uM (total IL15 MFI)
24 hour	0.035	0.255	0.063	0.75
24 hour (wash at 2 hours)	11.5	59.6	11.1	66.9
6 hours	0.021	0.81	0.030	0.88

Example 48. Regulated membrane bound IL15 expression *in vivo*

[00689] To evaluate regulation of membrane bound IL15 *in vivo*, 2 constructs were selected for evaluation *in vivo*. Four group of T cells were used for this study and are outlined in Table 34. In Table 31, "N" represents the number of mice in each group.

Table 34. T Cell Groups

Group	N	T Cells	Treatment
1	4	Untransduced	-
2	4	OT-IL15-071 (pELNS vector, EF1a promoter, membrane bound IL15 sequence from OT-IL15-008)	-
3	4	OT-IL15-073 (pELNS vector, EF1a promoter, membrane bound IL15 sequence from OT-IL15-009)	Vehicle
4	4	OT-IL15-073 (pELNS vector, EF1a promoter, membrane bound IL15 sequence from OT-IL15-009)	TMP

[00690] The T cells which were to be used as part of the *in vivo* study were evaluated 6 days post transduction, day of implant (day 9 post transduction) and 13 days post transduction and the cells in Groups 2-4 showed expression of the constructs.

[00691] T cells outlined in Table 31 were administered to mice by intravenous administration (3.9×10^6 cells per mouse implanted). On day 3 the mice were dosed with 500 mg/kg of TMP 3 times (4 hours between doses) and bled 2 hours after each dose. The mice were again bled on day 4, 24 hours after the first TMP dose.

[00692] Figures 43A-43C show the expression of membrane bound IL15, 2, 6, 10, and 24 hours after the first TMP dose, using IL15 staining (Figure 43A), IL15Ra staining (Figure 43B), and IL15/IL15Ra double ++ staining (Figure 43C). Figure 43D are FACS plots for each mouse 10 hours after the first TMP dose. Figure 43E shows the expression of membrane bound IL15 in blood 2, 6, 10, and 24 hours after the first TMP dose and Figure 43F shows the plasma TMP levels 2, 6, 10, and 24 hours after the first TMP dose.

Example 49. Effect of long term intraperitoneal (IP) or oral (PO) TMP dosing on T cell function

[00693] In this study, T cells transduced with OT-IL15-071 or OT-IL15-073 (no lentiBoost) were administered intravenously to mice (15×10^6 per mouse). 6 study groups were evaluated for this study: (1) untransduced, (2) OT-IL15-071 T cells, (3) OT-IL15-073 PO vehicle, (4) OT-IL15-073 PO TMP 500 mg/kg), (5) OT-IL15-073 IP vehicle, and (6) OT-IL15-073 IP TMP 300 mg/kg. The study design is shown in Table 35. PO dosing is 500 mg/kg TMP in 0.1M citrate and IP dosing is 300 mg/kg TMP lactate in water.

Table 35. Study Design

Timepoint	Dose	Sample Collection
Day -3	Inject T cells in mice by IV administration	-
Day 0	PO 1x or IP 1x	-
4 hours	PO 1x	-
6 hours	-	Bleed (survival)
24 hours	PO 2x or IP 1x	Bleed (survival)
Day 2	PO 1x or IP 1x	-
Day 3	PO 1x or IP 1x	-
Day 4	PO 2x or IP 1x	-
120 hours	PO 2x or IP 1x	Bleed (survival)
126 hours	-	Bleed (survival)
Day 6	PO 2x or IP 1x	-
Day 7	PO 2x or IP 1x	-
Day 8	-	Bleed (survival)
Day 19	-	Bleed (survival)
Day 25	-	Bleed (terminal)

[00694] The regulated expression in blood was analyzed 6 hours and 24 hours after the first dose, and 6 hours after the 5th dose.

[00695] OT-IL15-071 showed expression of membrane bound IL15 and the untransduced control did not show any expression.

[00696] Regulation of membrane bound IL15 was seen with repeat PO and IP dosing. As seen in Figure 44, regulated expression of membrane bound IL15 was detected 6 hours after the first dose on day 0, and 6 hours after dosing on day 5 (126 hrs) with both PO and IP dosing. There was no increase in expression in mice treated with vehicle.

[00697] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible

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interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

[00698] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

[00699] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[00700] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLWS:

1. A composition comprising a polynucleotide encoding an effector module, said effector module comprising a stimulus response element (SRE) operably linked to at least one payload, wherein the SRE comprises a destabilizing domain (DD), said DD comprising amino acids 2 to 187 of a human dihydrofolate reductase (hDHFR; SEQ ID NO. 2) and further comprising a Y122I mutation in the amino acid at position 122 (Y122) of SEQ ID NO. 2.

2. The composition of claim 1, wherein the DD further comprises:
(i) a Q36K mutation in the amino acid at position 36 (Q36) of SEQ ID NO. 2;
(ii) an A125F mutation in the amino acid at position 125 (A125) of SEQ ID NO. 2; or
(iii) a N65F mutation in the amino acid at position 65 (N65) of SEQ ID NO. 2 and a substitution of F or K at the amino acid position 36 (Q36) of SEQ ID NO. 2.

3. The composition of claim 1 or 2, wherein the SRE is responsive to at least one stimulus.

4. The composition of claim 3, wherein the stimulus is selected from the group consisting of Trimethoprim (TMP) and Methotrexate (MTX).

5. The composition of any one of claims 1-4, wherein the DDstabilizes the at least one payload by a stabilization ratio of 1 or more, wherein the stabilization ratio comprises the ratio of expression, function or level of the payload in the presence of the stimulus to the expression, function or level of the payload in the absence of the stimulus.

6. The composition of any one of claims 1-5, wherein the DD destabilizes the at least one payload by a destabilization ratio between 0 and 0.09, wherein the destabilization ratio comprises the ratio of expression, function or level of the payload in the absence of the stimulus specific to the SRE to the expression, function or level of the payload that is expressed constitutively, and in the absence of the stimulus specific to the SRE.

7. The composition of any one of claims 1-6, wherein the at least one payload is an immunotherapeutic agent.

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8. The composition of claim 7, wherein the immunotherapeutic agent is selected from a chimeric antigen receptor (CAR), a cytokine, and a cytokine-cytokine receptor fusion polypeptide.

9. The composition of claim 8, wherein the immunotherapeutic agent is a chimeric antigen receptor (CAR) that comprises (a) an extracellular target moiety; (b) a transmembrane domain; (c) an intracellular signaling domain; and (d) optionally, one or more co-stimulatory domains.

10. The composition of claim 8 or 9, wherein the CAR is a CD19 CAR.

11. The composition of claim 8, wherein the cytokine is IL12 or IL15.

12. The composition of claim 8, wherein the cytokine-cytokine receptor fusion polypeptide is a IL15-IL15Ra fusion polypeptide.

13. The composition of any one of claims 1-12, wherein the effector module further comprises a second payload, wherein the second payload is a chimeric antigen receptor (CAR).

14. The composition of any one of claims 1-13, wherein the effector module further comprises a signal peptide, a regulatory sequence, a linker, a protein tag, and/or a protein cleavage site.

15. The composition of any one of claims 1-14, wherein the polynucleotide is a DNA molecule or a RNA molecule.

16. The composition of claim 15, wherein the polynucleotide is an RNA molecule and said RNA molecule is a messenger RNA (mRNA).

17. The composition of any one of claims 1-16, wherein the polynucleotide is chemically modified.

18. The composition of any one of claims 1-17, wherein the polynucleotide further comprises a promoter, a linker, a signal peptide, a tag, a cleavage site and/or a targeting peptide.

19. A vector comprising the polynucleotide of any one of claims 1-18.

20. The vector of claim 19, wherein the vector is a viral vector or a plasmid.

21. The vector of claim 20, which is a viral vector and wherein the viral vector is a retroviral vector, a lentiviral vector, a gamma retroviral vector, a recombinant AAV vector, an adeno viral vector, or an oncolytic viral vector.

22. The vector of claim 21, which is a retroviral vector or a lentiviral vector.

23. A cell which expresses the effector module as defined in any one of claims 1-18, and/or is infected or transfected with the vector of any one of claims 19-22.

24. The cell of claim 23, wherein said cell is an immune cell for adoptive cell transfer (ACT).

25. The cell of claim 23 or 24, wherein said cell is a CD8+ T cell, a CD4+ T cell, a helper T cell, a natural killer (NK) cell, a NKT cell, a cytotoxic T lymphocyte (CTL), a tumor infiltrating lymphocyte (TIL), a memory T cell, a regulatory T (Treg) cell, a cytokine-induced killer (CIK) cell, a dendritic cell, a human embryonic stem cell, a mesenchymal stem cell, a hematopoietic stem cell, or a mixture thereof.

26. The cell of any one of claims 23-25, wherein said cell is a T cell modified to express a chimeric antigen receptor (CAR).

27. A pharmaceutical composition comprising:
(i) the composition of any one of claims 1-18;
(ii) the vector of any one of claims 19-22; or
(iv) the cell of any one of claims 23-26; and
a pharmaceutically acceptable excipient.

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28. A method of producing a modified cell, said method comprising introducing into a cell the composition of any one of claims 1-18 or the vector of any one of claims 19-22.

29. A kit comprising a stimulus when used in modulating expression, function, and/or level of a payload in the cell of any one of claims 23-26, wherein the stimulus response element (SRE) is responsive to the stimulus; wherein the stimulus is a small molecule that binds to the SRE; and wherein the expression, function, and/or level of the payload is modulated in response to the stimulus.

30. The composition of any one of claims 1-18, a composition comprising the vector of any one of claims 19-22, or a composition comprising the cell of any one of claims 23-26, for treating a disease in a subject in need thereof, wherein the composition is used in combination with a stimulus, wherein the stimulus response element (SRE) is responsive to the stimulus; and wherein expression of the payload is modulated in response to the stimulus to thereby treat the disease.

31. The composition according to claim 30, wherein the stimulus is selected from Trimethoprim (TMP) or Methotrexate (MTX).

32. The composition of any one of claims 1-18, a composition comprising the vector of any one of claims 19-22, or a composition comprising the cell of any one of claims 23-26 for the treatment of a disease or for inducing an immune response in a subject.

33. The composition of any one of claims 1-18, a composition comprising the vector of any one of claims 19-22, or a composition comprising the cell of any one of claims 23-26 for treatment of cancer.

34. A method of modulating expression, function, and/or level of a payload in the cell of any one of claims 23-26, said method comprising administering to the cell a stimulus, wherein the stimulus response element (SRE) is responsive to the stimulus and wherein the expression, function, and/or level of the payload is modulated in response to the stimulus.

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35. The composition of any one of claims 1-18, a composition comprising the vector of any one of claims 19-22, or a composition comprising the cell of any one of claims 23-26, for use in a method of treating a disease in a subject in need thereof, characterized in that the composition is administered to the subject in combination with a stimulus,
wherein the SRE is responsive to the stimulus and wherein expression of the payload is modulated in response to the stimulus to thereby treat the disease.

36. The composition for use according to claim 35, wherein the stimulus is selected from Trimethoprim (TMP) or Methotrexate (MTX).

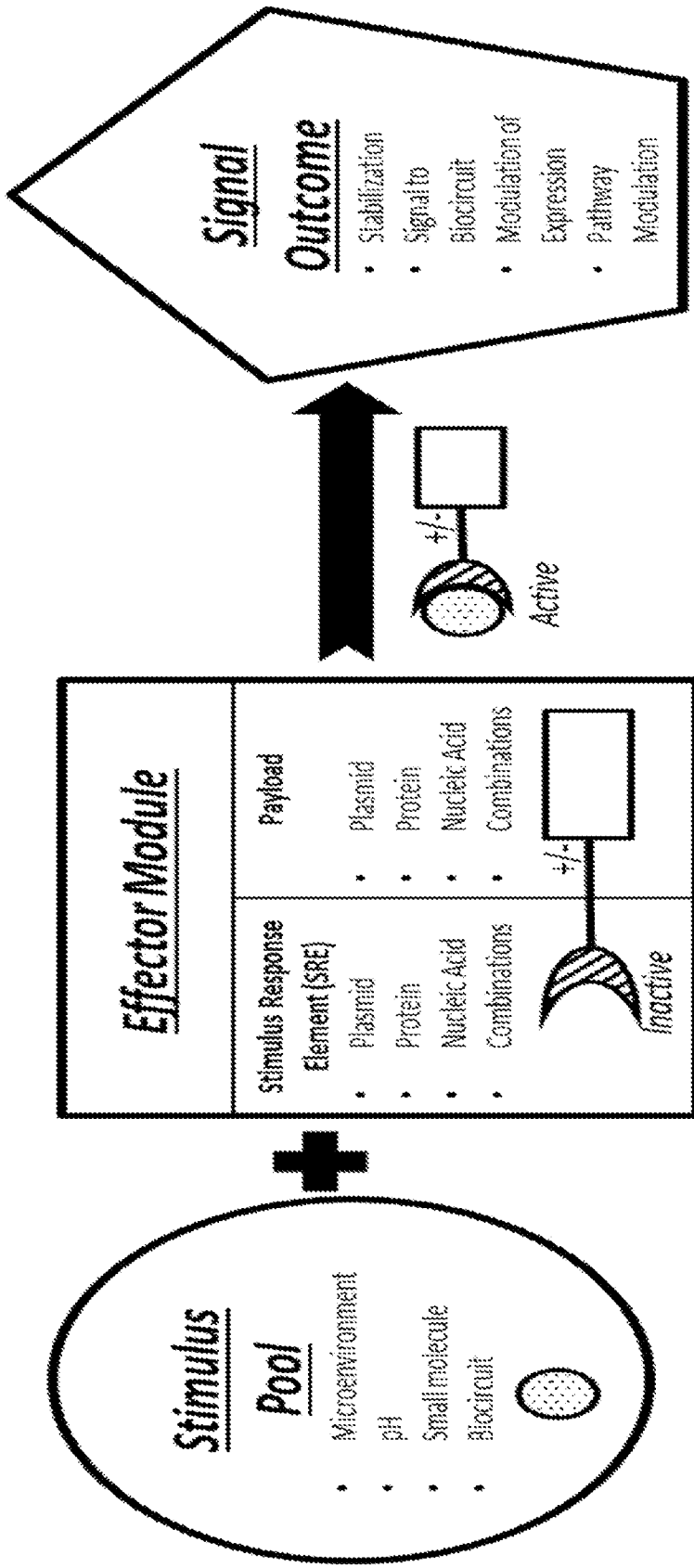

Signal Outcome
• Stabilization
• Signal to Biocircuit
• Modulation of Expression
• Pathway Modulation
+/-
Active
Effector Module
Stimulus Response Element (SRE)
• Plasmid
• Protein
• Nucleic Acid
• Combinations
Payload
• Plasmid
• Protein
• Nucleic Acid
• Combinations
+/-
Inactive
Stimulus Pool
• Microenvironment
• pH
• Small molecule
• Biocircuit

Figure 1

Figure 2

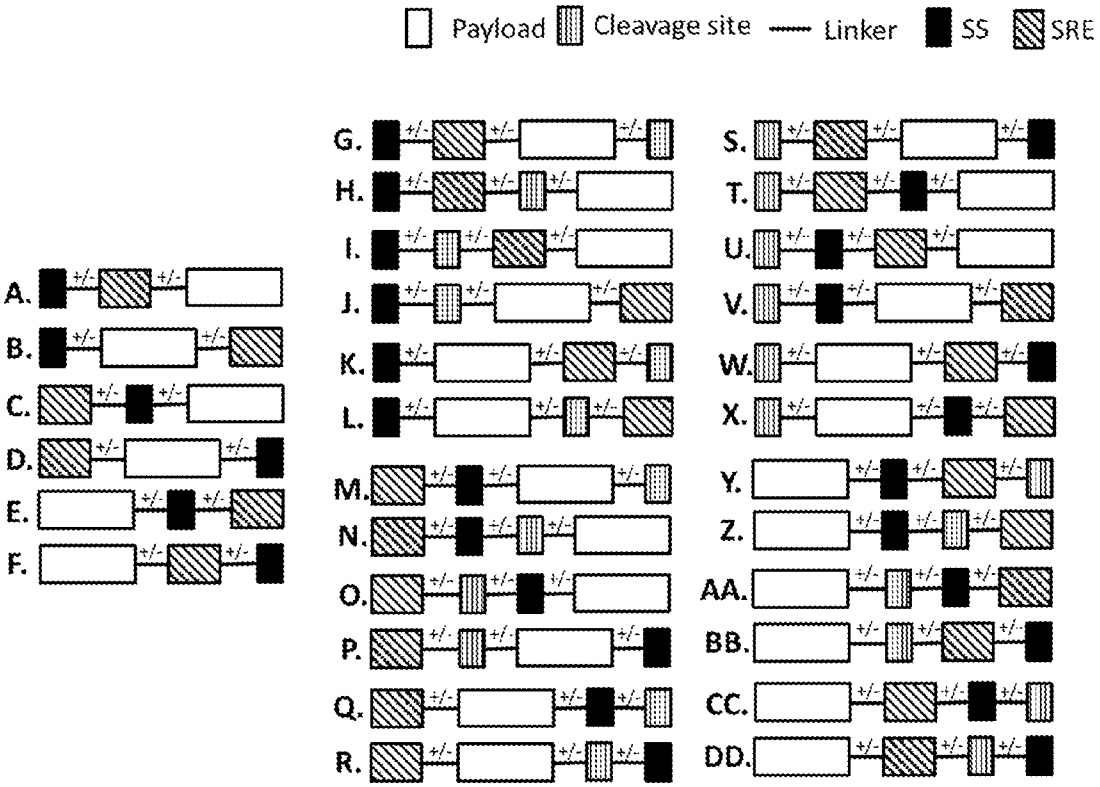


Figure 3

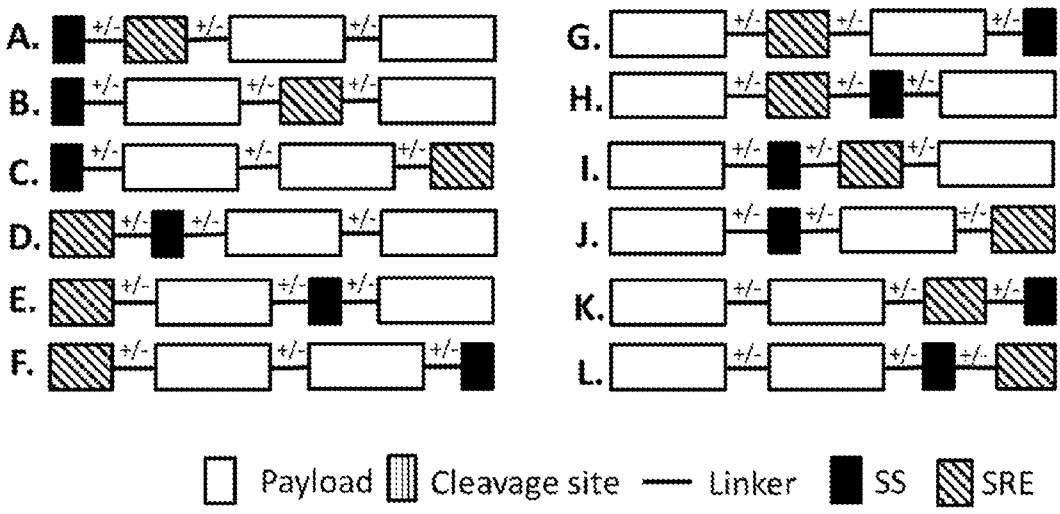


Figure 4

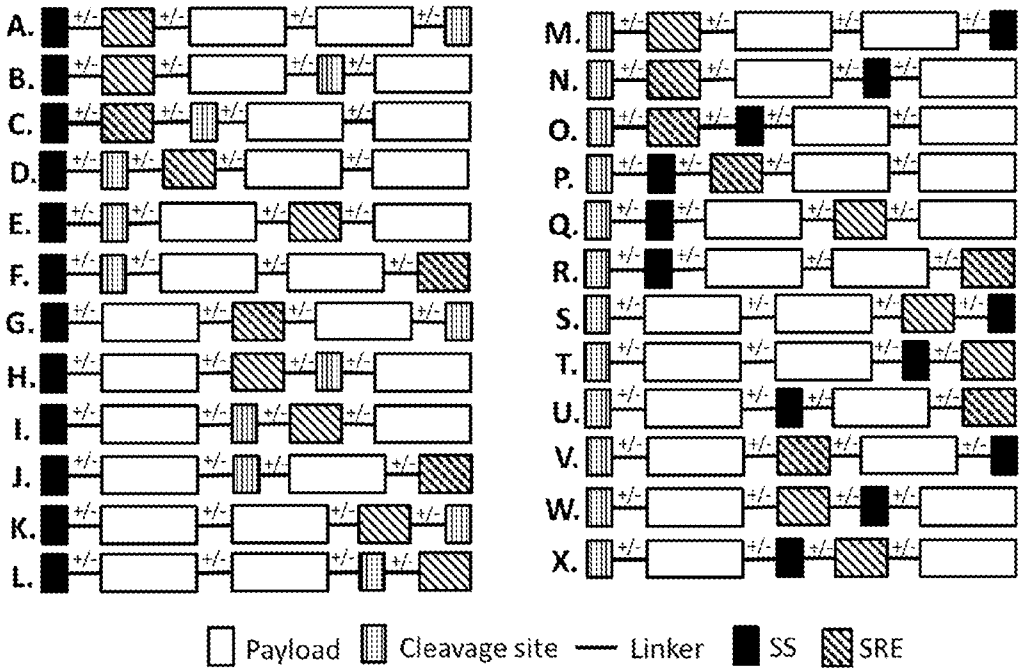


Figure 5

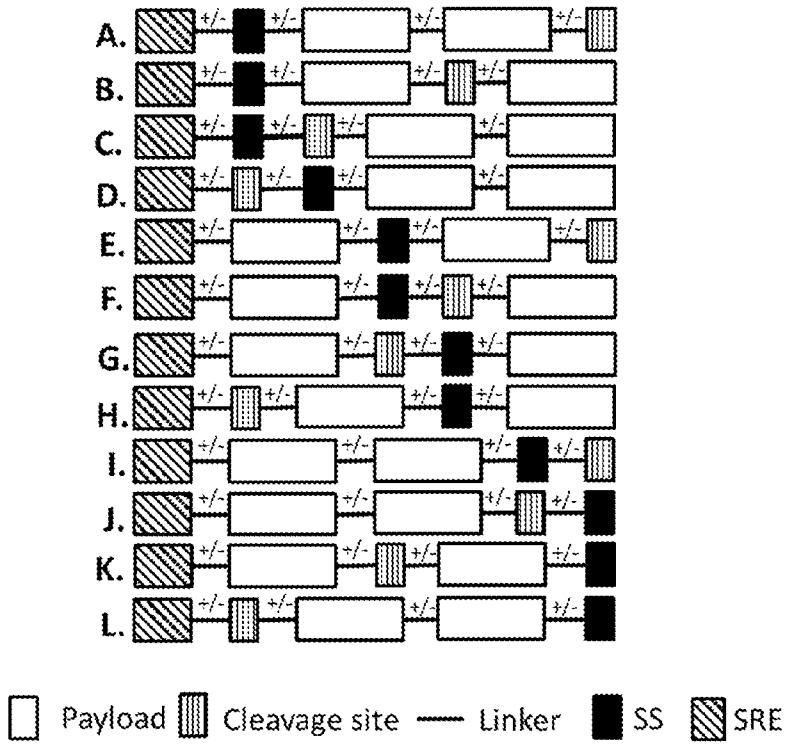


Figure 6

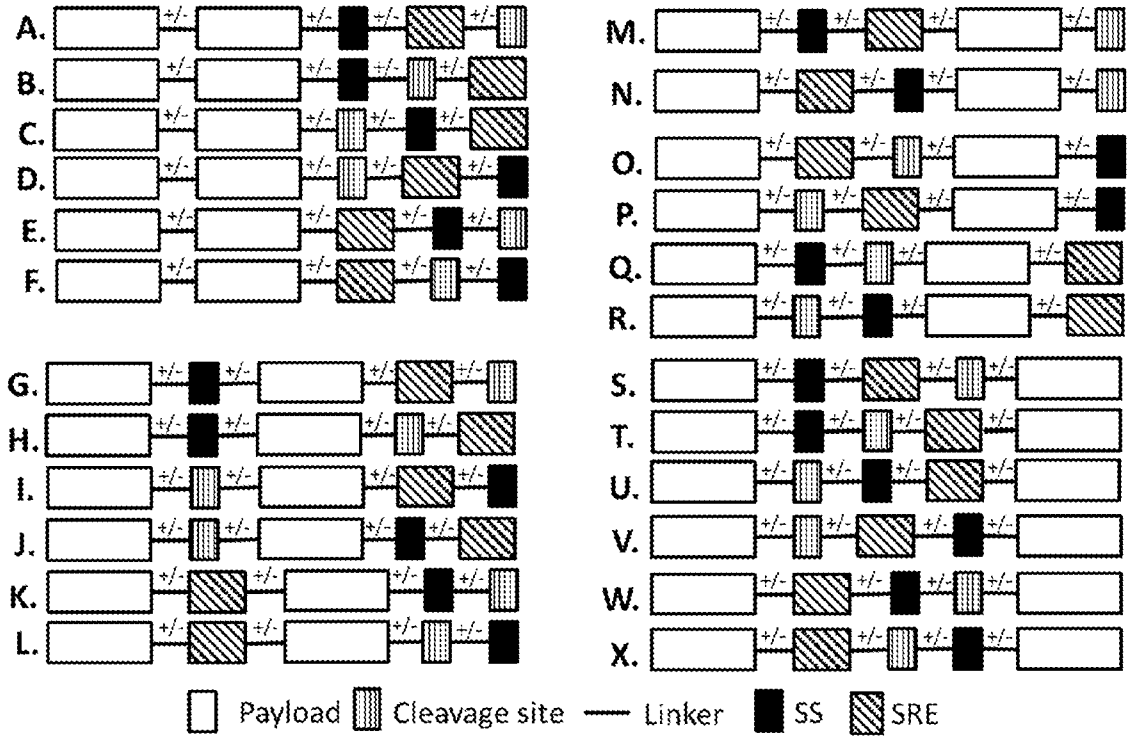


Figure 7

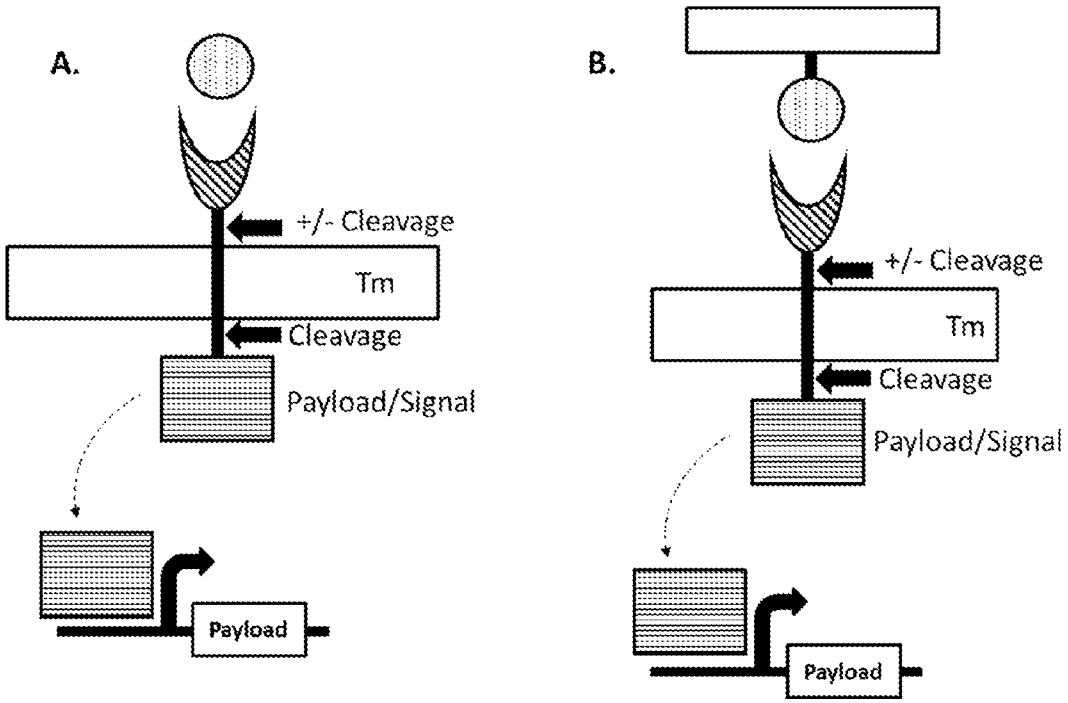


Figure 8

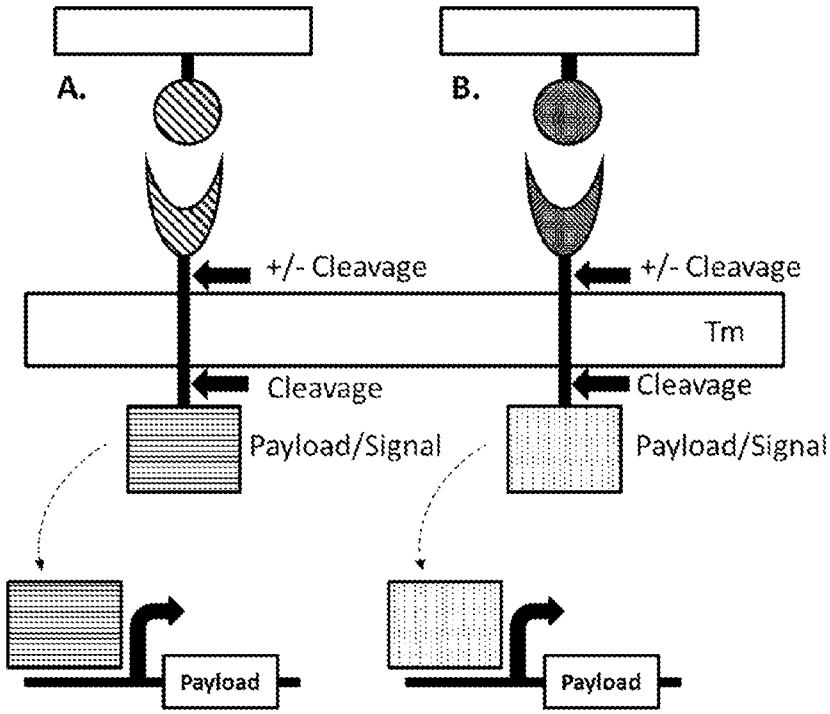


Figure 9

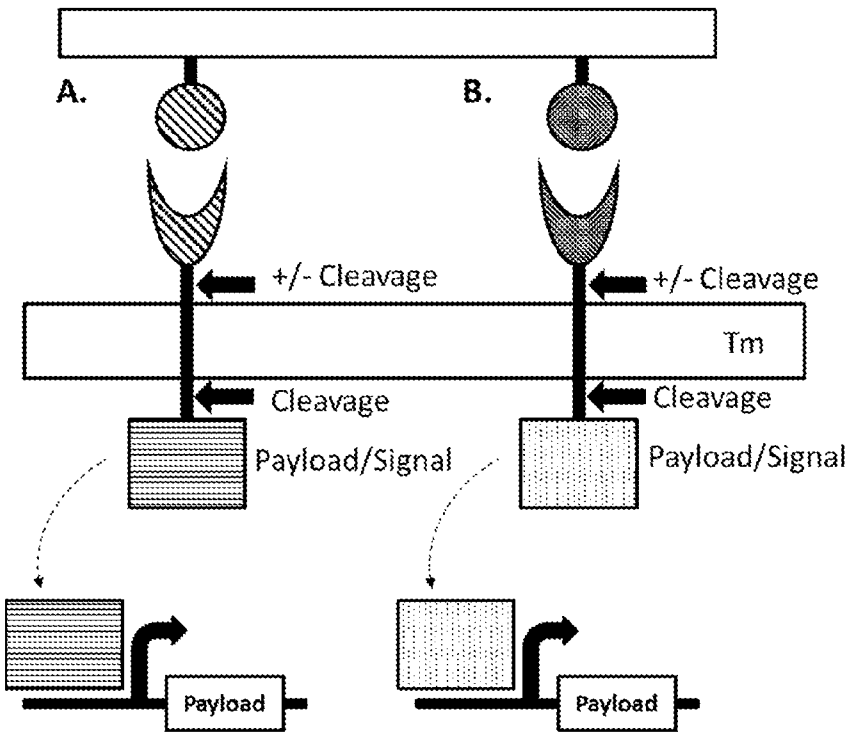


Figure 10

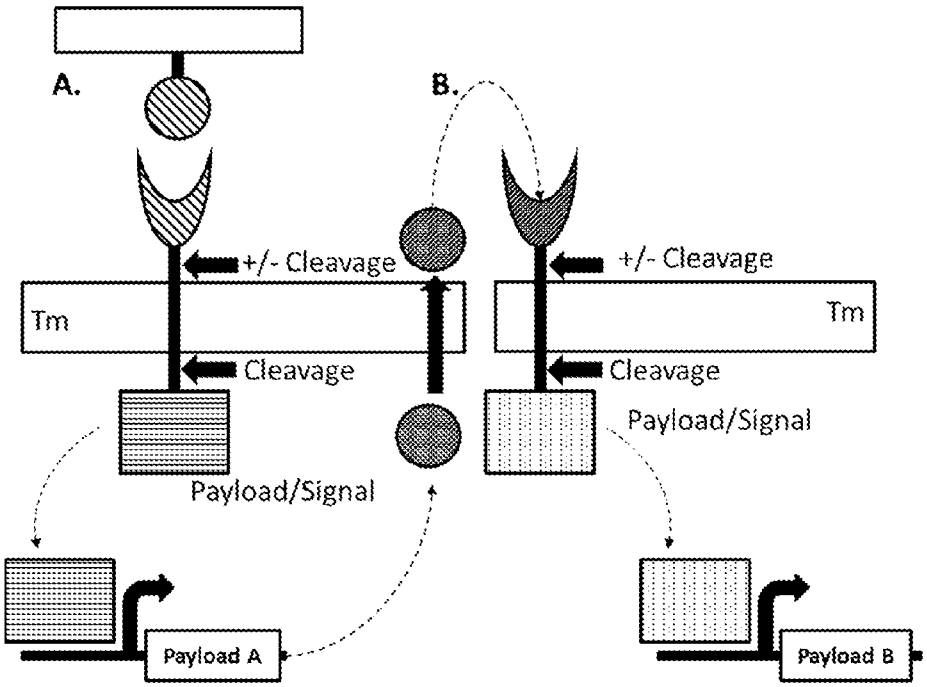


Figure 11

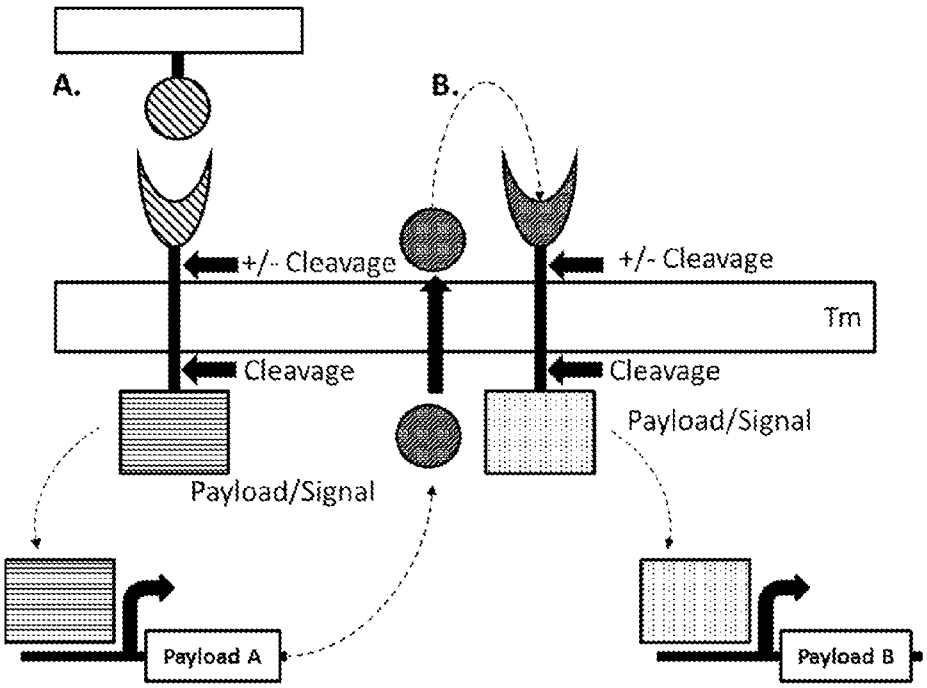


Figure 12

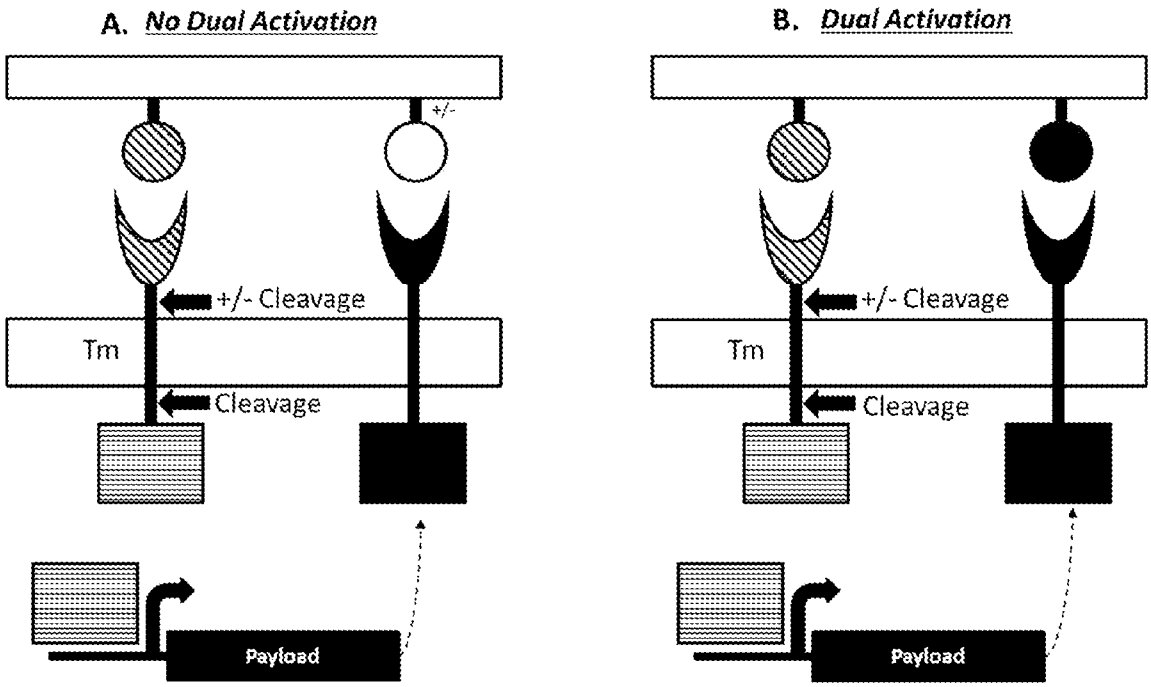


Figure 13

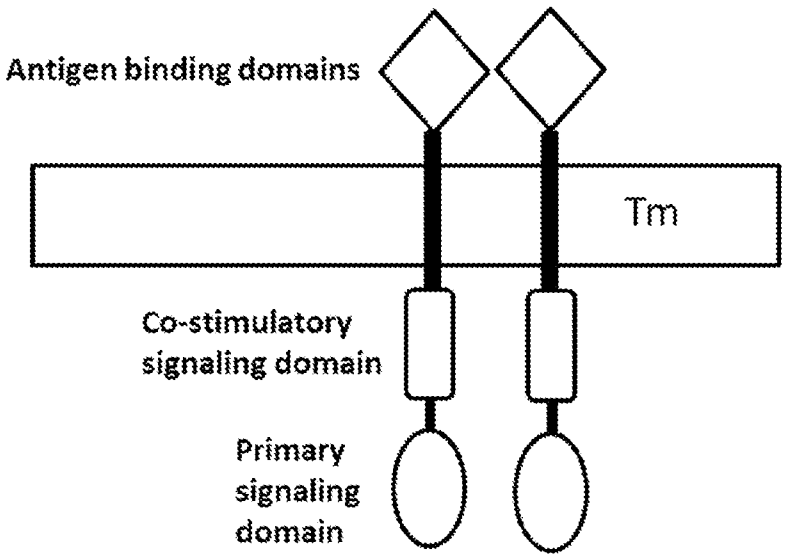


Figure 14

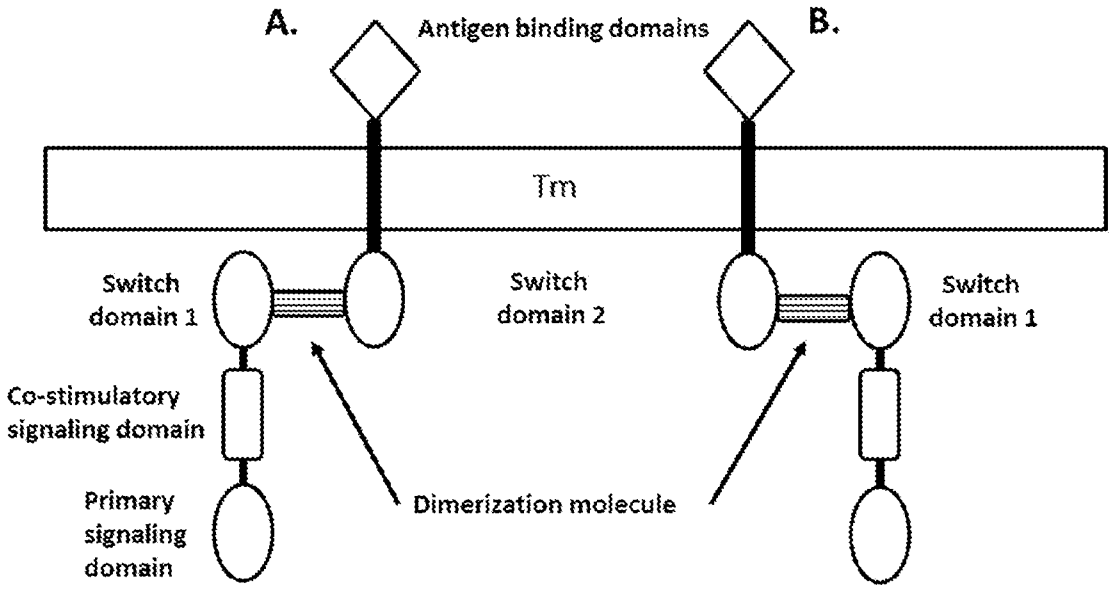


Figure 15

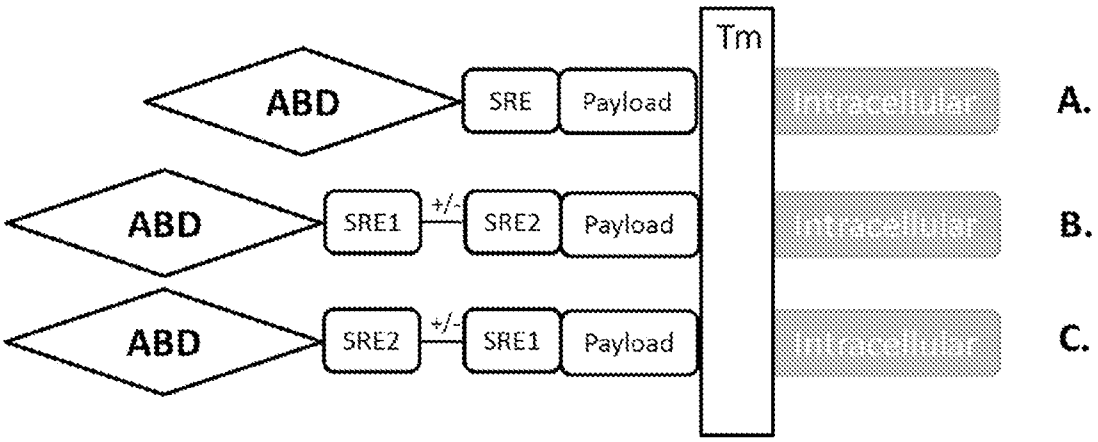


Figure 16

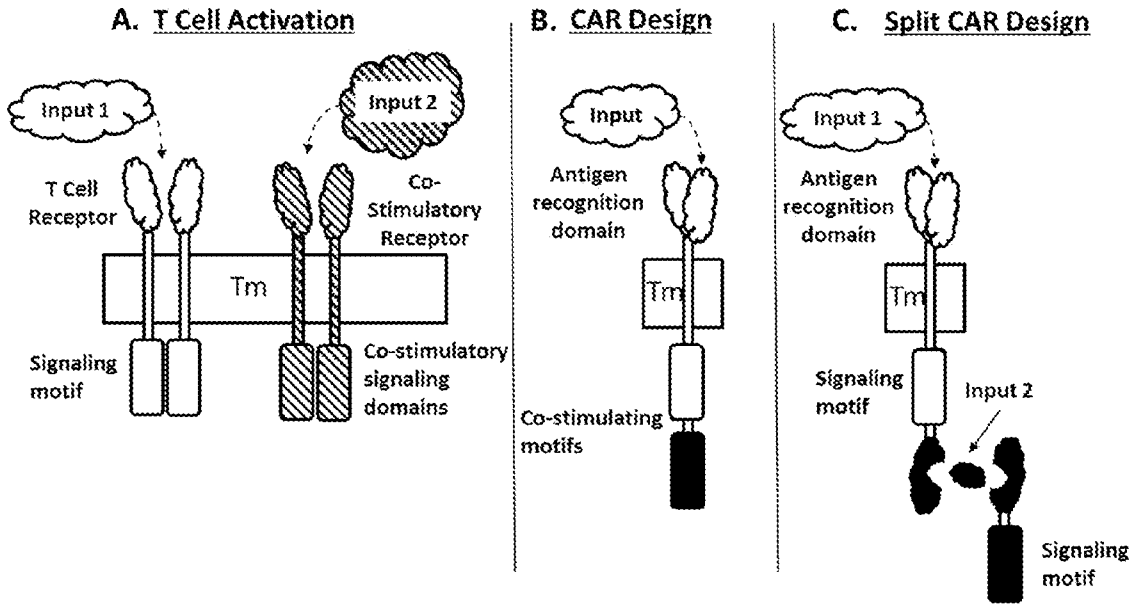


Figure 17

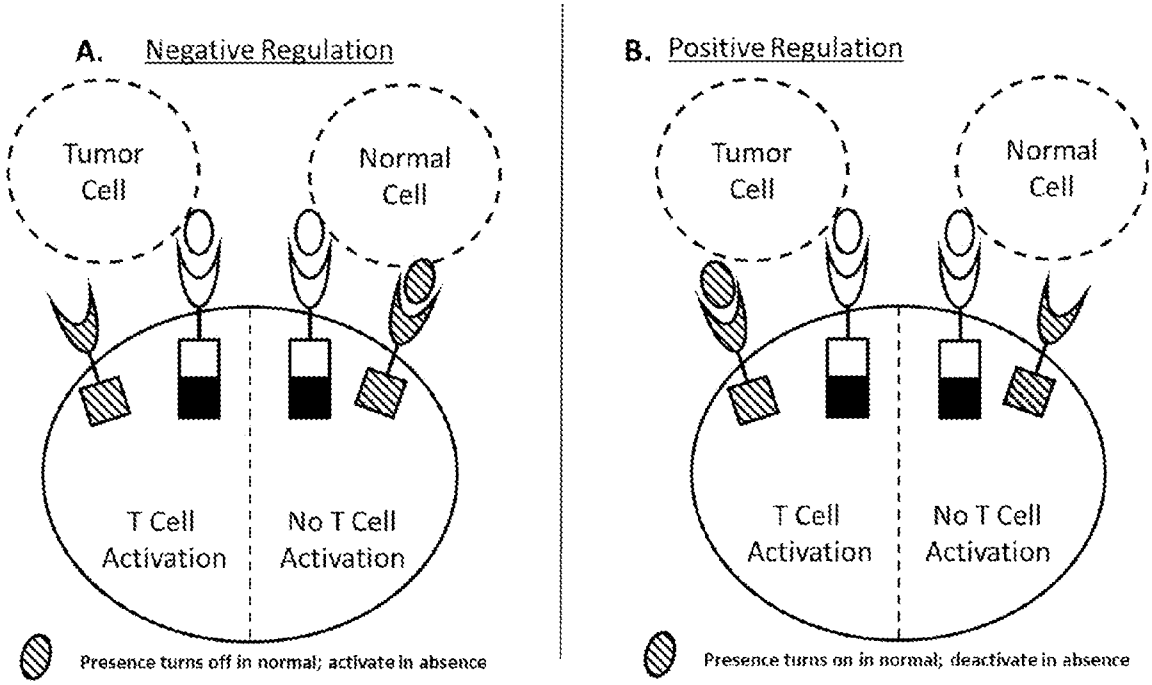


Figure 18

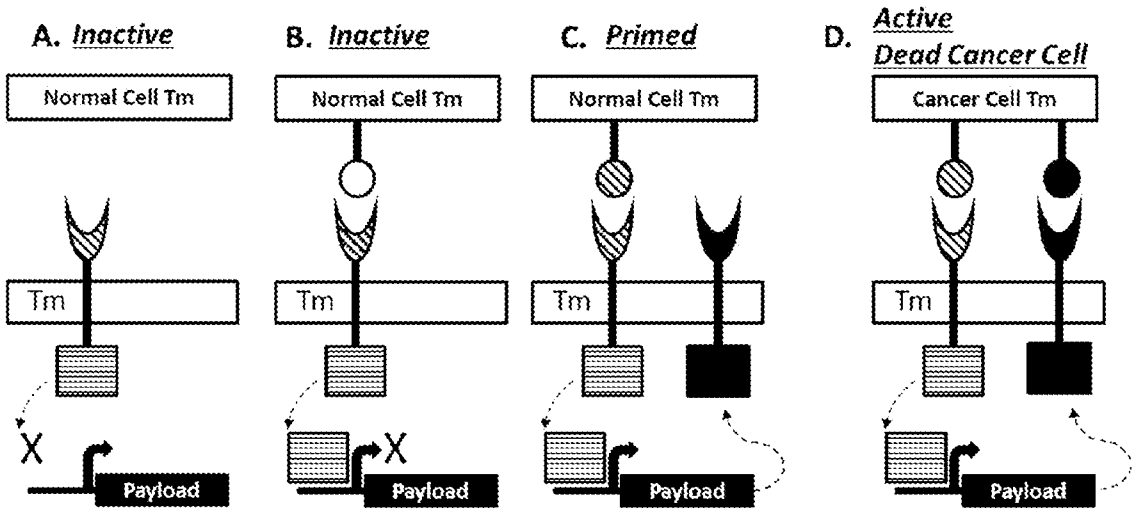


Figure 19A

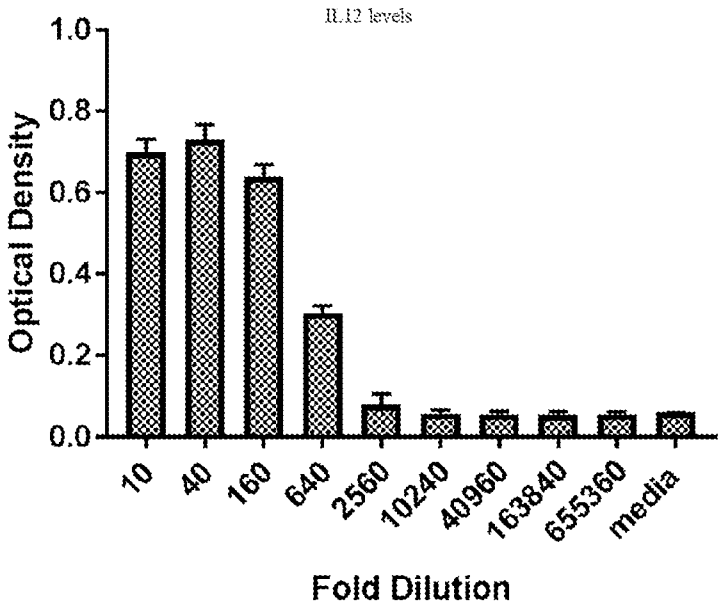


Figure 19B

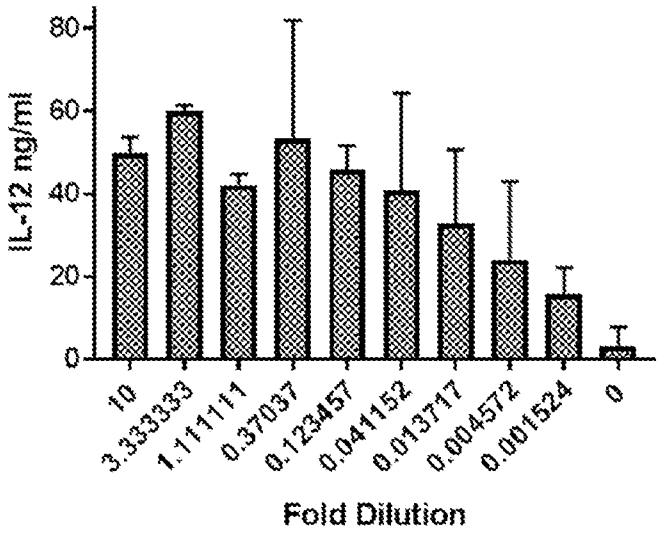
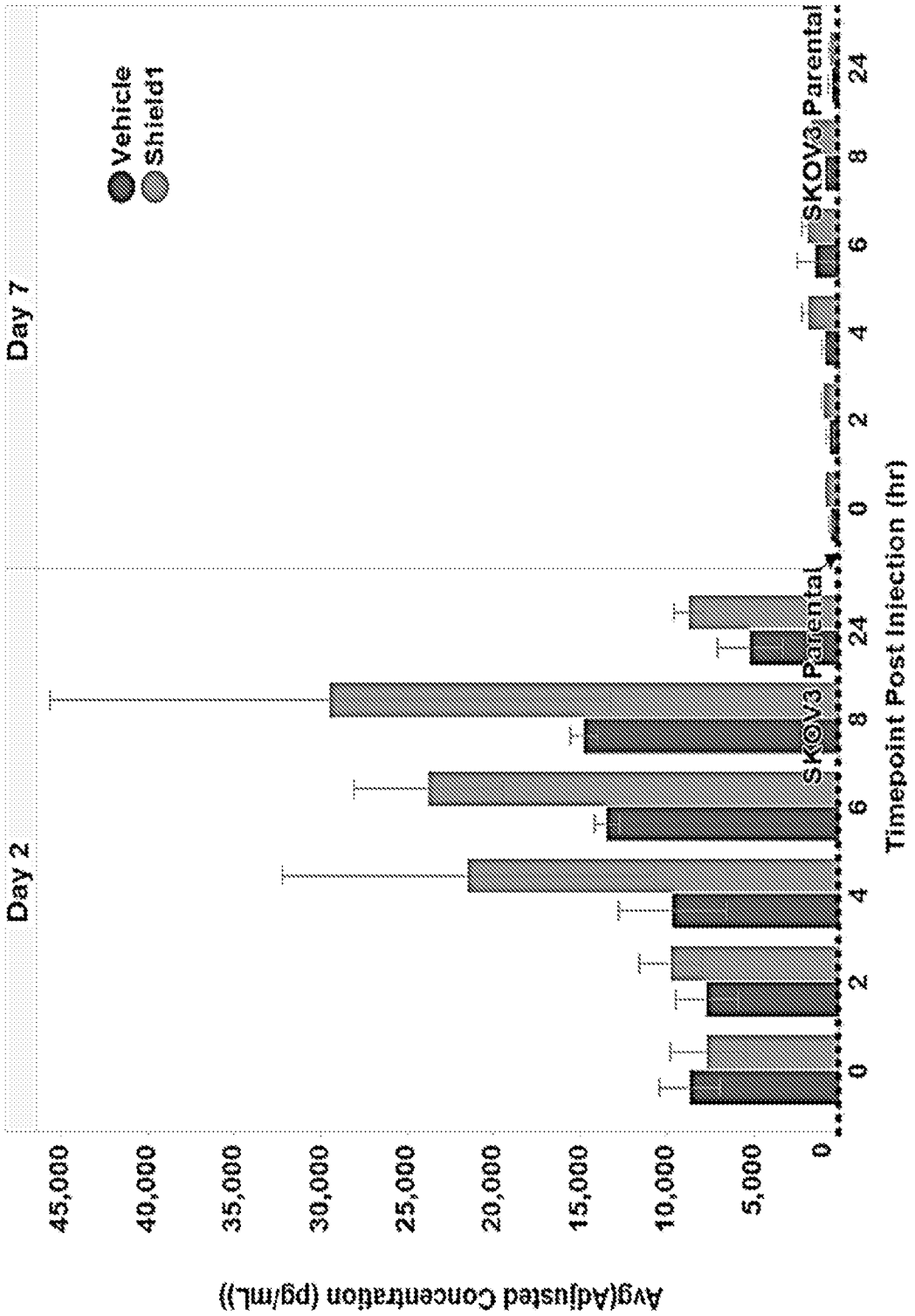

IL-12 ng/ml
80
60
40
20
0
10
3.333333
1.111111
0.37037
0.123457
0.041152
0.013717
0.004572
0.001524
0
Fold Dilution

Figure 19C


Day 2
Day 7
Vehicle
Shield1
SKOV3 Parental
SKOV3 Parental
Timepoint Post Injection (hr)
Avg(Adjusted Concentration (pg/mL))
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
0
2
4
6
8
24
0
2
4
6
8
24

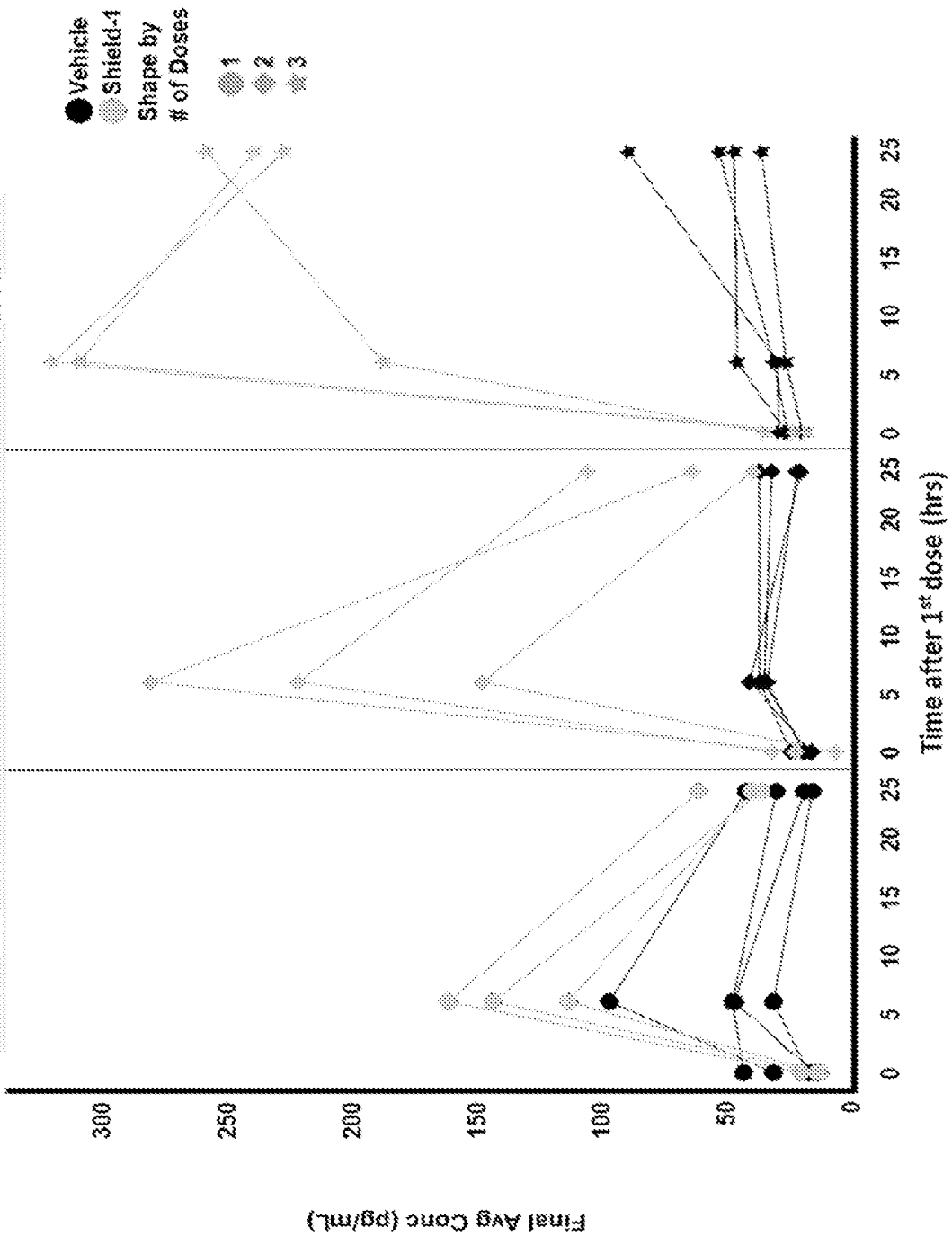

Vehicle
Shield-1
Shape by
# of Doses
1
2
3
1 dose
2 doses
3 doses
Final Avg Conc (pg/mL)
Time after 1st dose (hrs)

Figure 19D

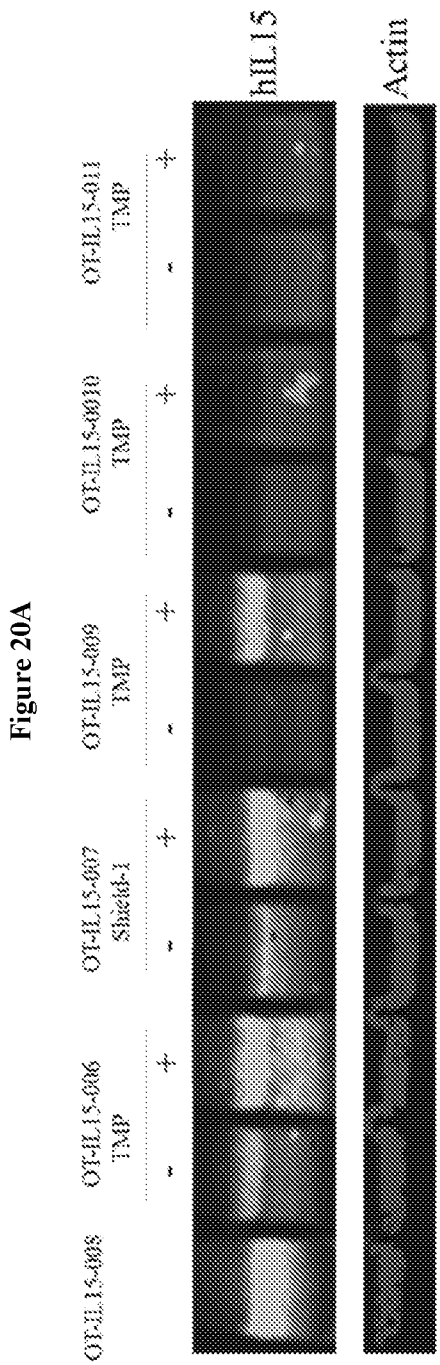

hIL15
Actin
OT-IL15-008
OT-IL15-006 TMP
OT-IL15-007 Shield-1
OT-IL15-009 TMP
OT-IL15-0010 TMP
OT-IL15-011 TMP
- + - + - + - +

Figure 20A

Figure 20B

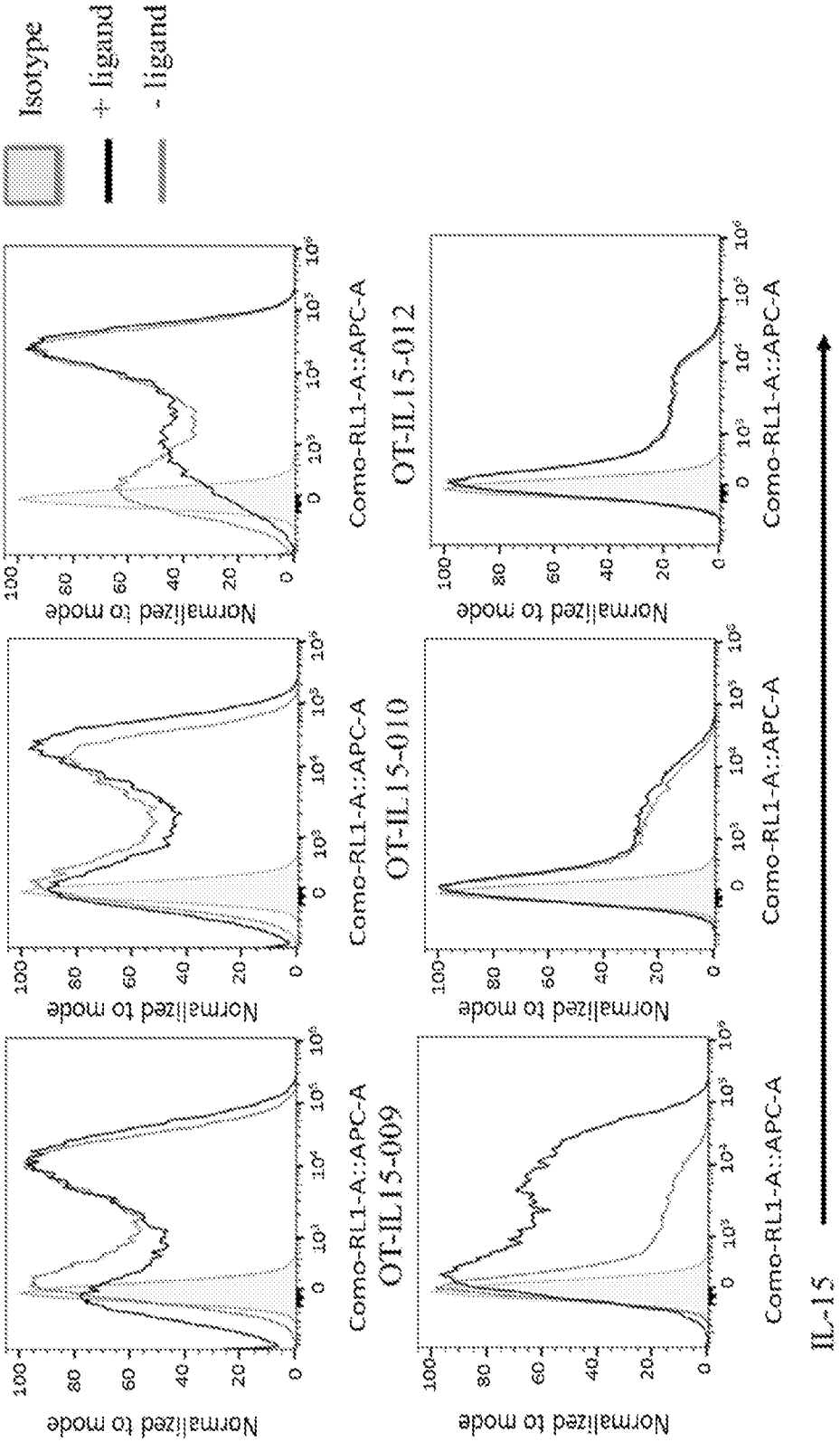

Isotype
+ ligand
- ligand
OT-IL15-006
OT-IL15-007
OT-IL15-008
OT-IL15-009
OT-IL15-010
OT-IL15-012
Como-RL1-A::APC-A
Normalized to mode
IL-15

Figure 20C

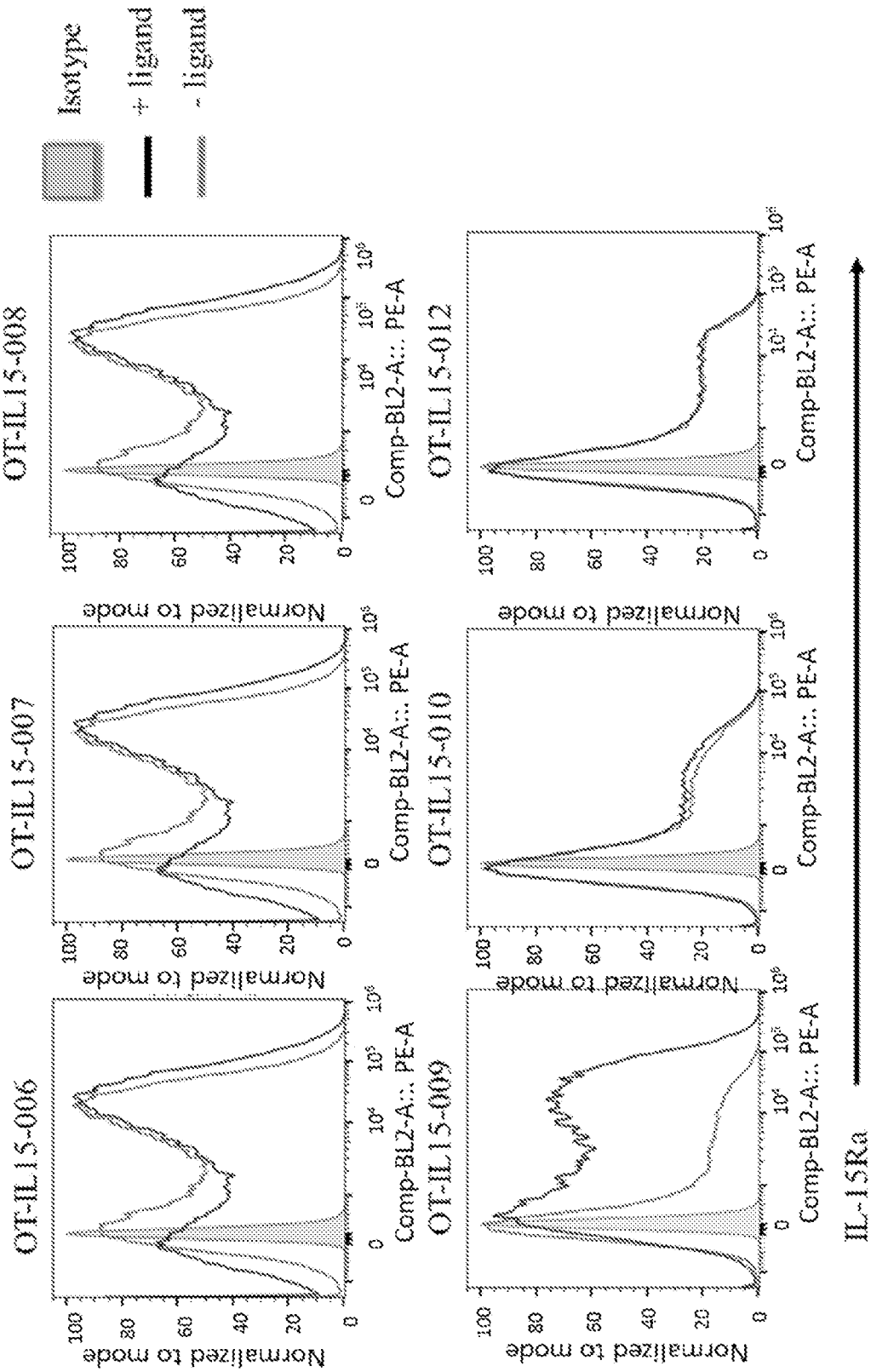

Isotype
+ ligand
- ligand
OT-IL15-006
OT-IL15-007
OT-IL15-008
OT-IL15-009
OT-IL15-010
OT-IL15-012
Normalized to mode
Comp-BL2-A::: PE-A
IL-15Rα

Figure 20D

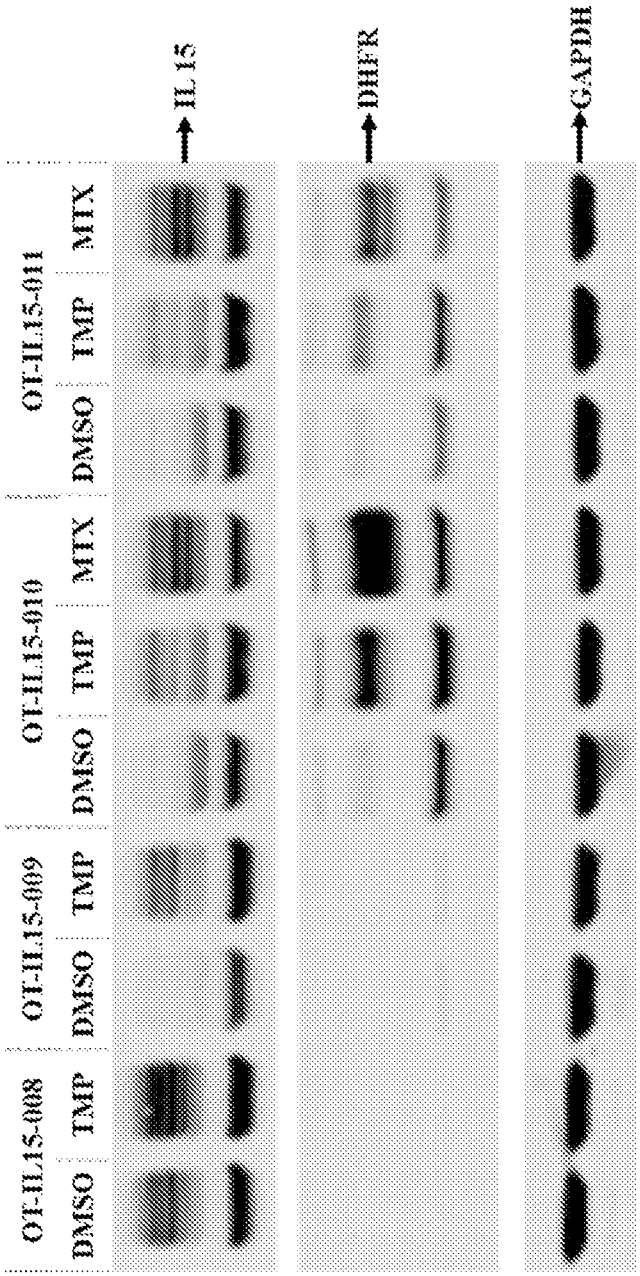

IL 15
DHFR
GAPDH
OT-IL15-008
DMSO
TMP
OT-IL15-009
DMSO
TMP
OT-IL15-010
DMSO
TMP
MTX
OT-IL15-011
DMSO
TMP
MTX

Figure 21A

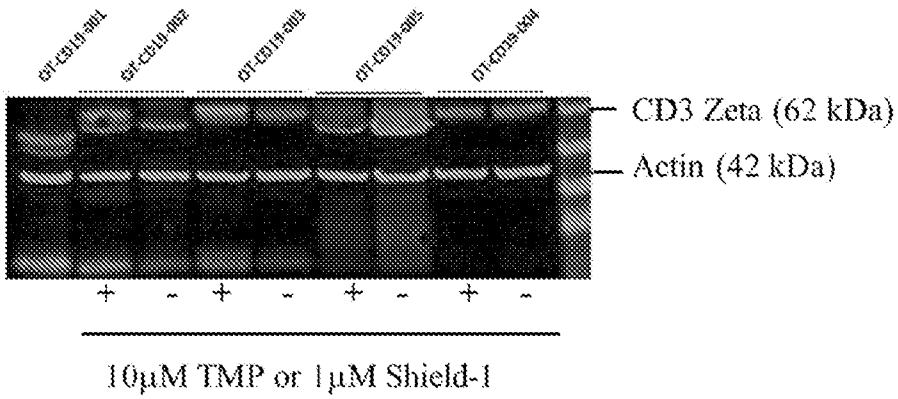


Figure 21B

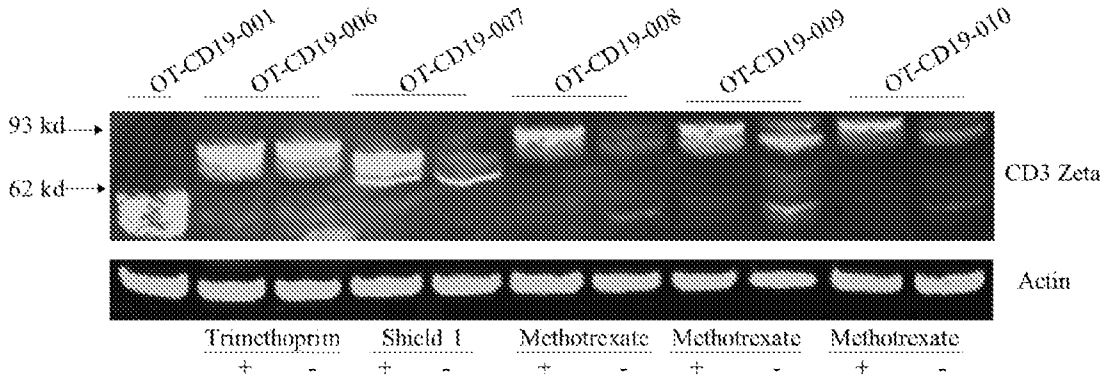


Figure 21C

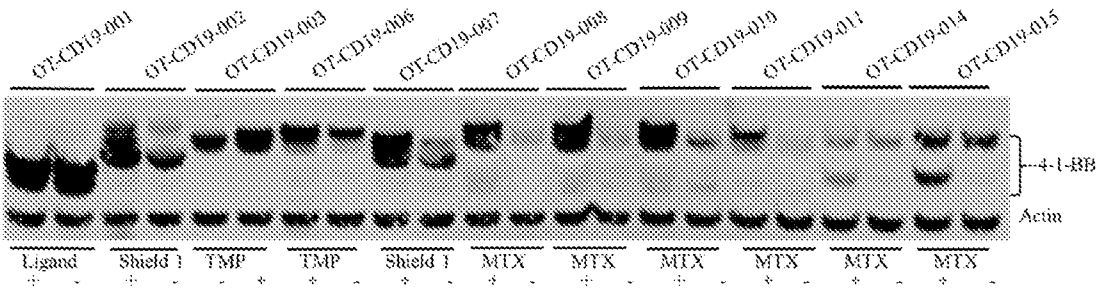


Figure 21D

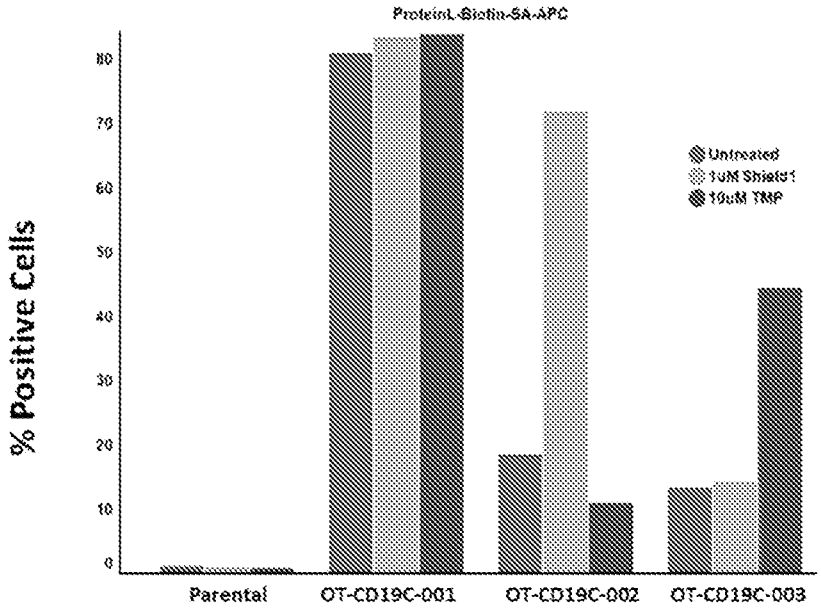


Figure 22

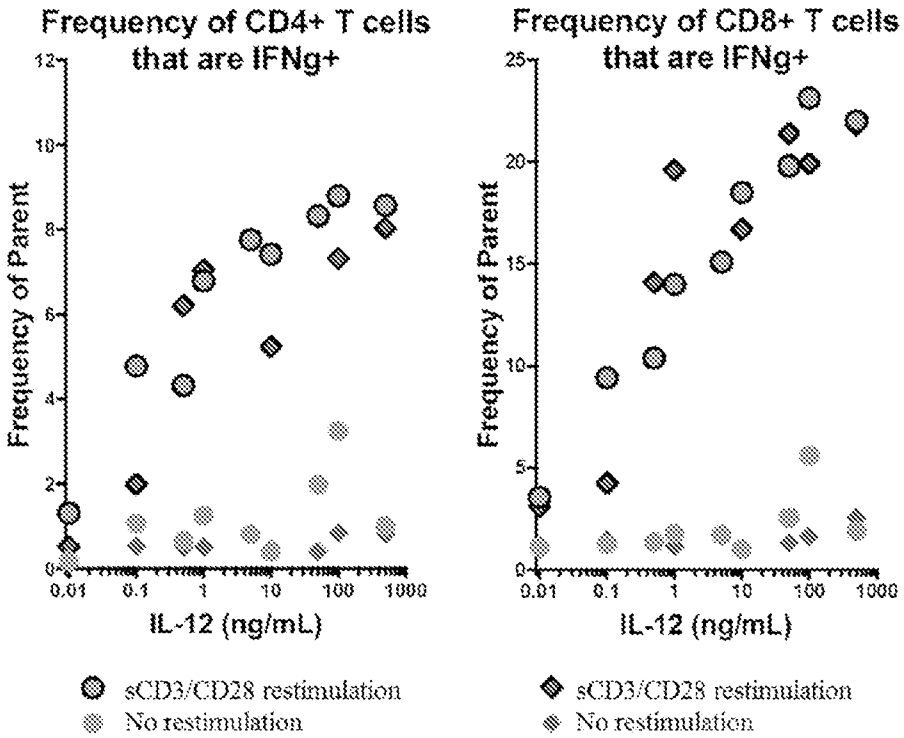


Figure 23A

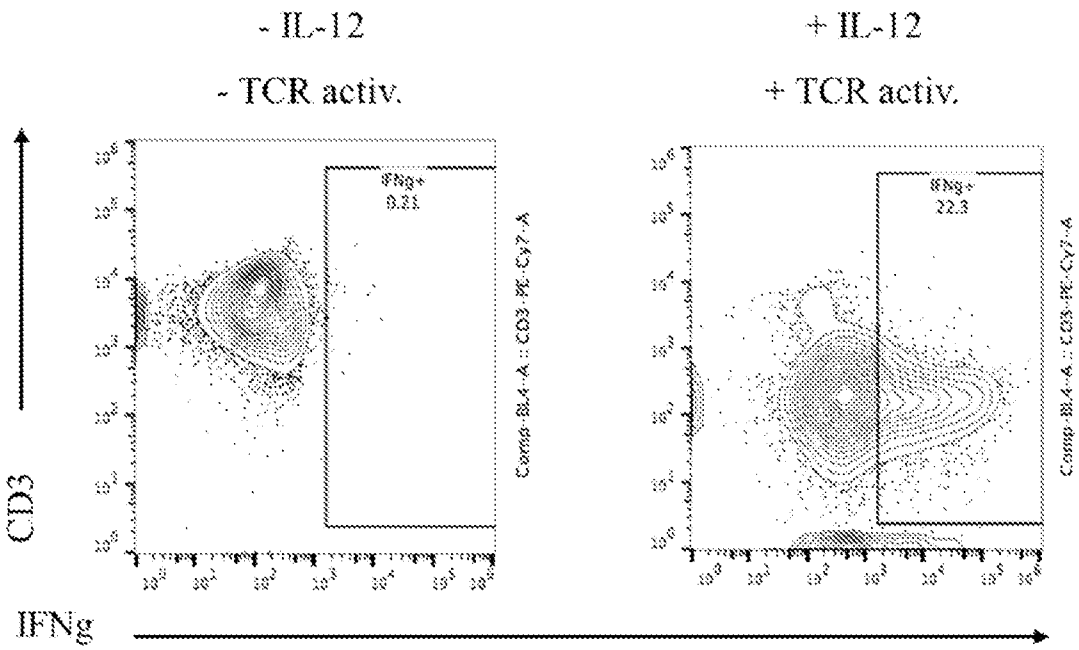


Figure 23B

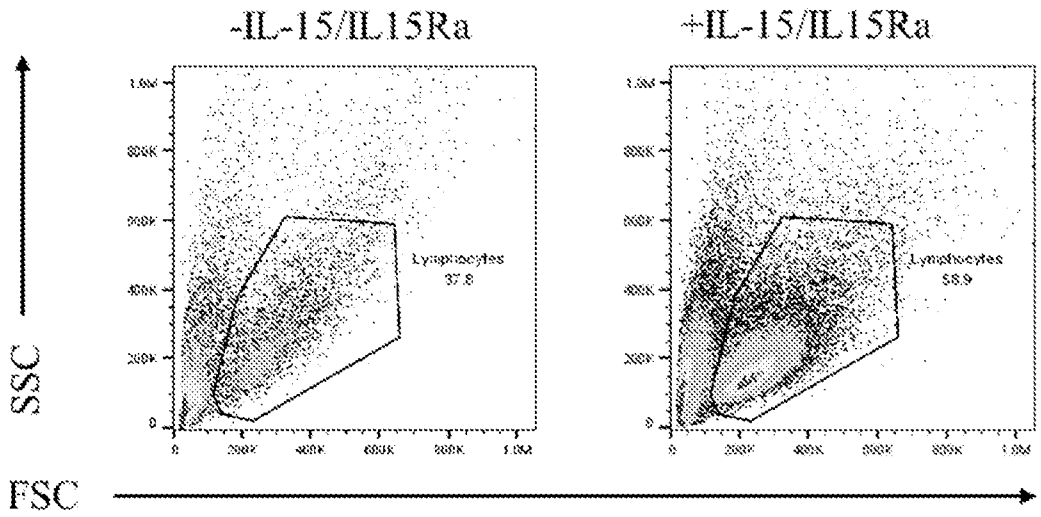


Figure 23C

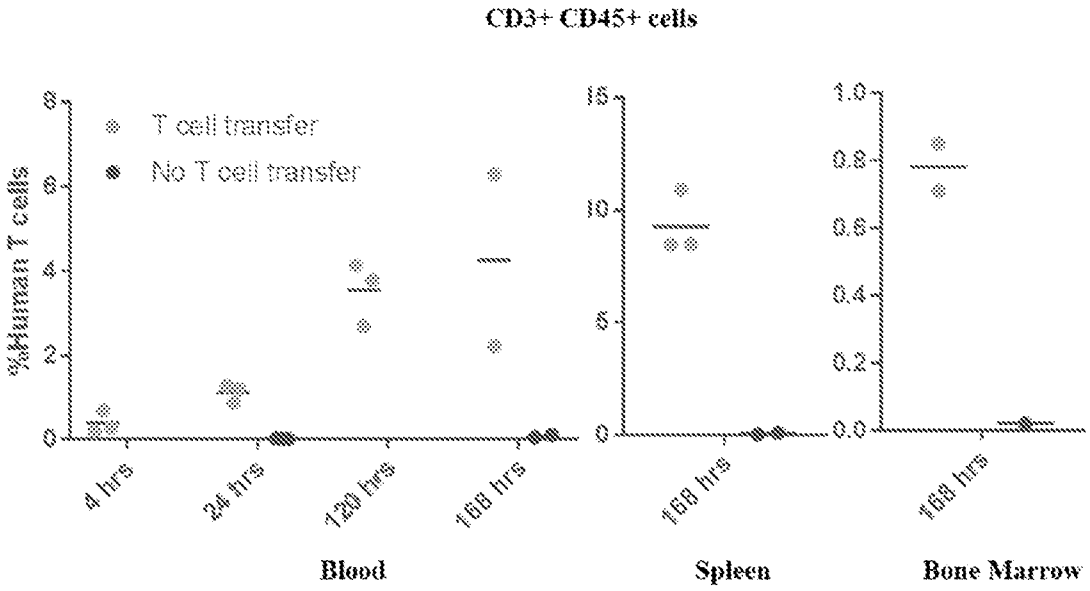


Figure 23D

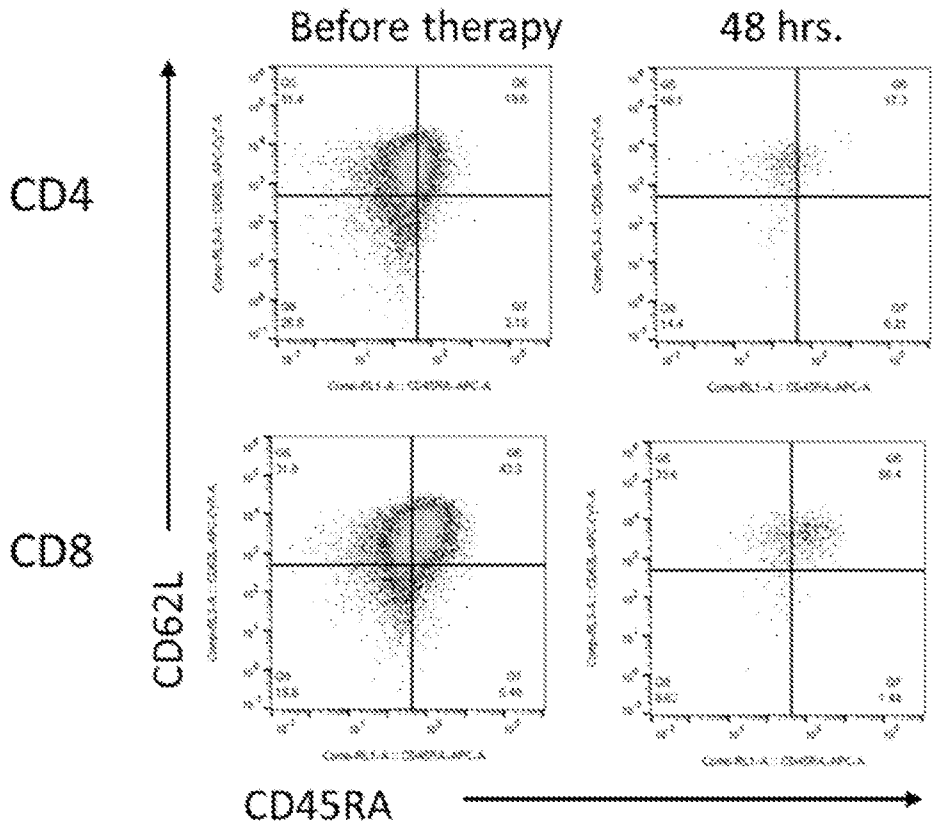


Figure 24A

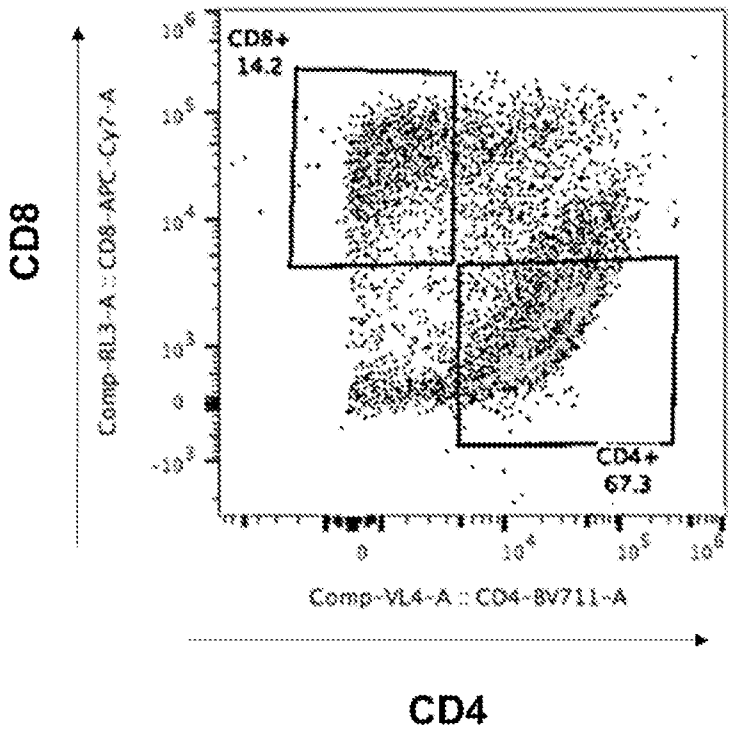


Figure 24B

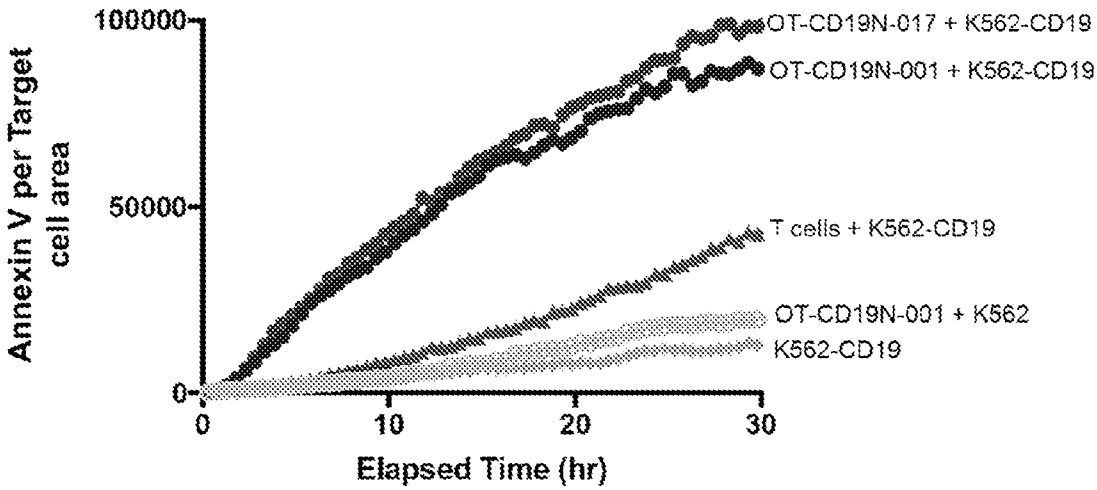


Figure 25A

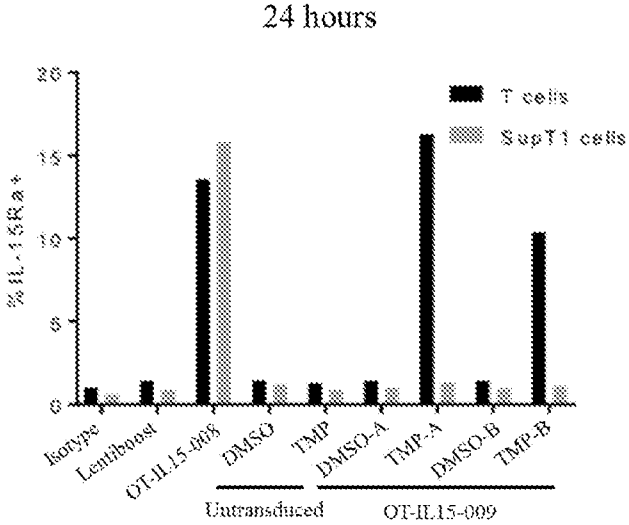


Figure 25B

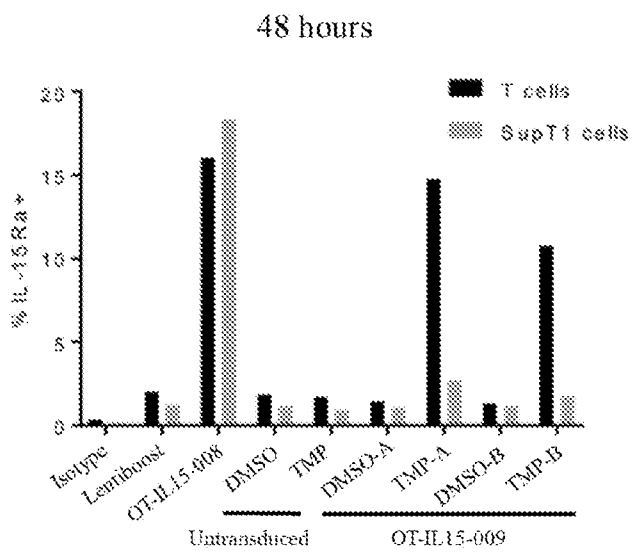


Figure 25C

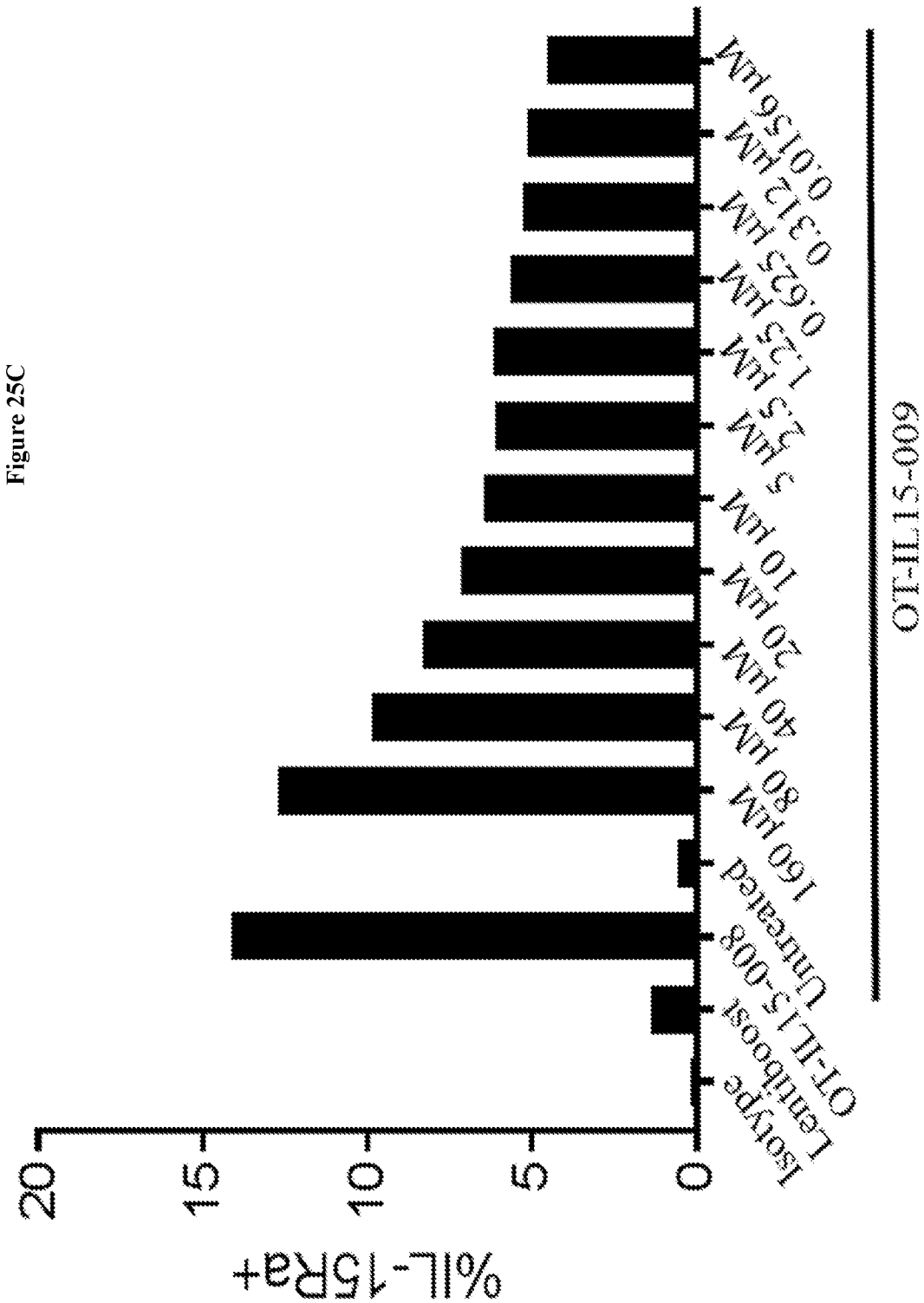


Figure 25C
%IL-15Ra+
20
15
10
5
0
Isotype
Lenzilumab
OT-IL15-008
Unmeated
160 µM
80 µM
40 µM
20 µM
10 µM
5 µM
2.5 µM
1.25 µM
0.625 µM
0.312 µM
0.0156µM
OT-IL15-009

Figure 26

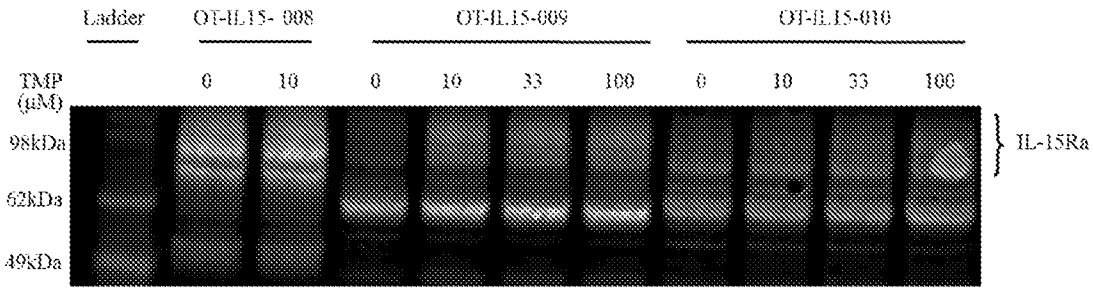

Ladder
OT-IL15- 008
OT-IL15-009
OT-IL15-010
TMP (μM)
0
10
0
10
33
100
0
10
33
100
98kDa
62kDa
49kDa
IL-15Ra

Figure 27A

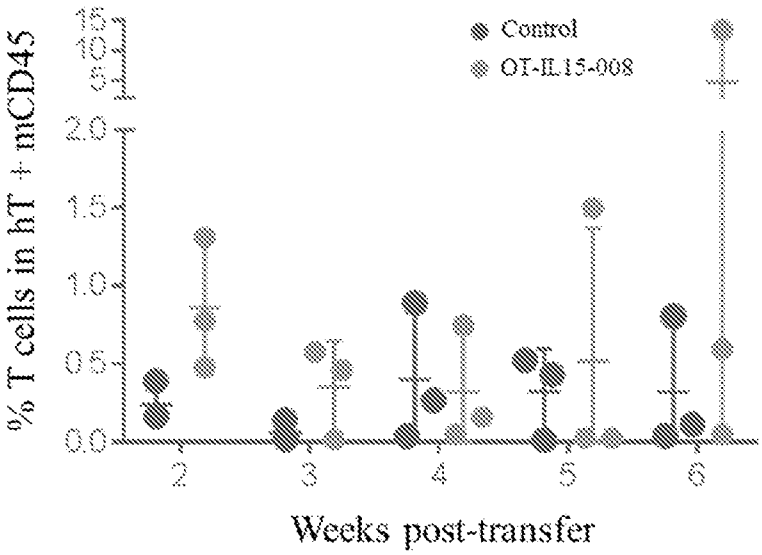


Figure 27B

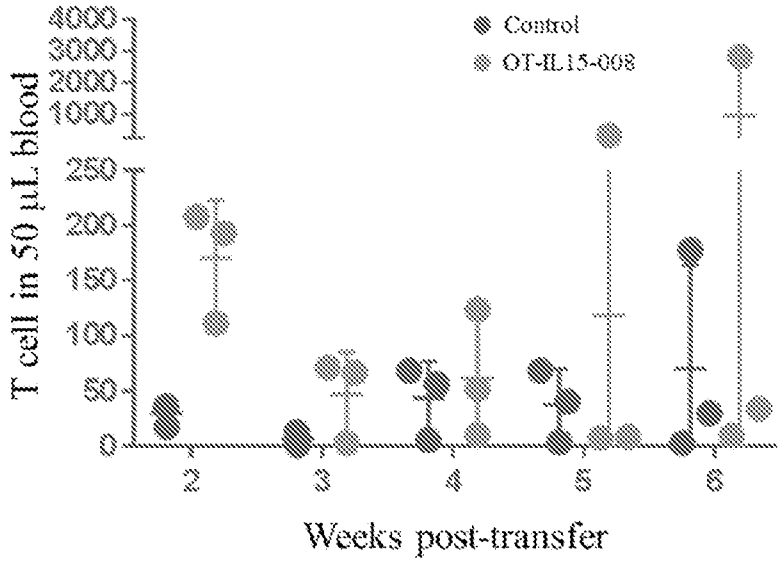


Figure 27C

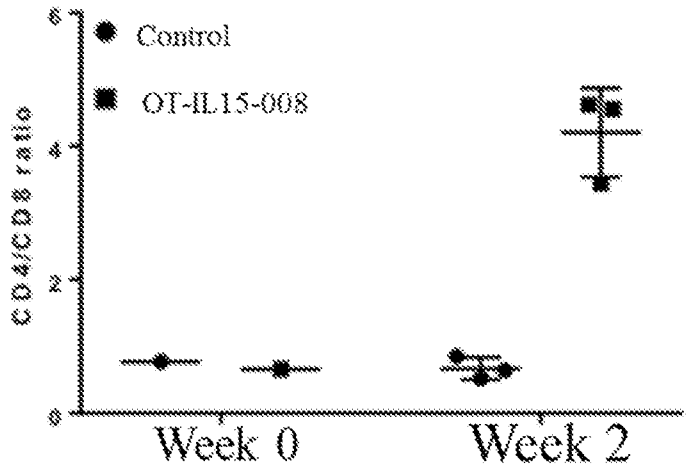


Figure 27D

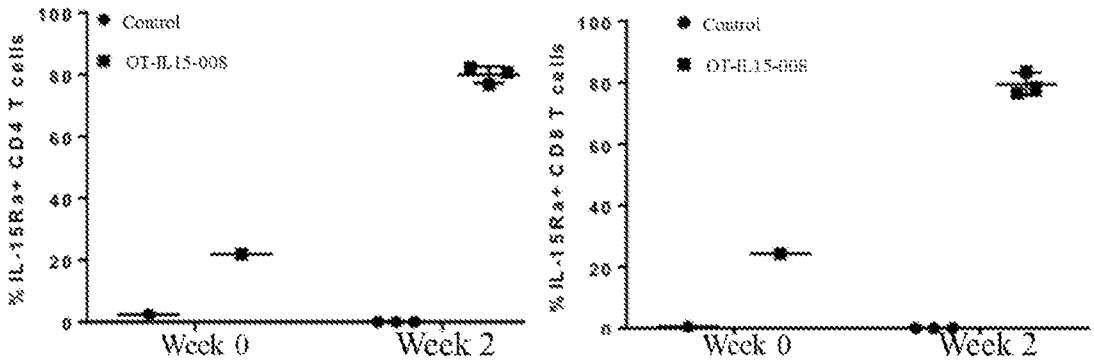


Figure 28A

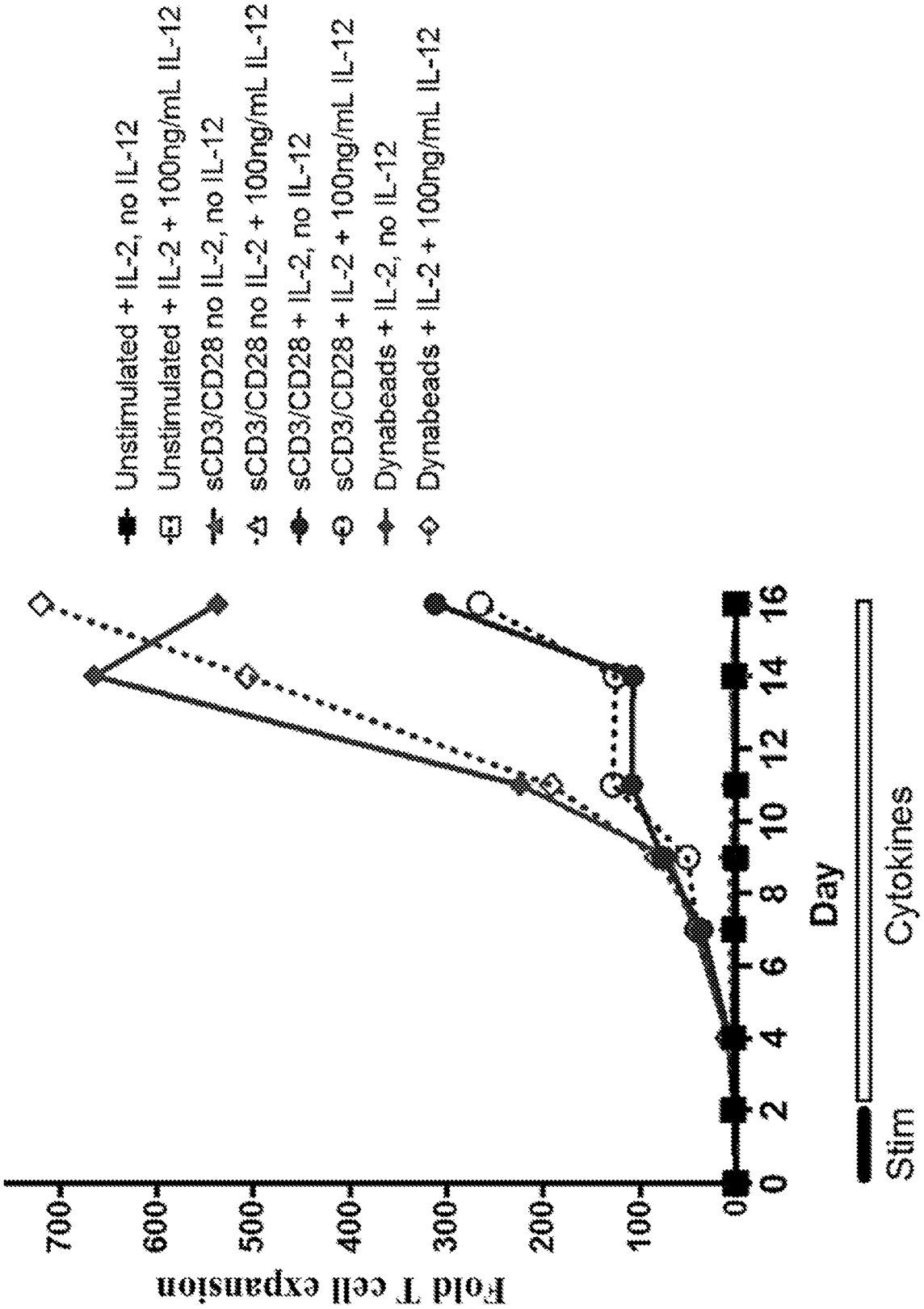

Unstimulated + IL-2, no IL-12
Unstimulated + IL-2 + 100ng/mL IL-12
sCD3/CD28 no IL-2, no IL-12
sCD3/CD28 no IL-2 + 100ng/mL IL-12
sCD3/CD28 + IL-2, no IL-12
sCD3/CD28 + IL-2 + 100ng/mL IL-12
Dynabeads + IL-2, no IL-12
Dynabeads + IL-2 + 100ng/mL IL-12
Fold T cell expansion
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
14
16
Day
Stim
Cytokines

Figure 28B

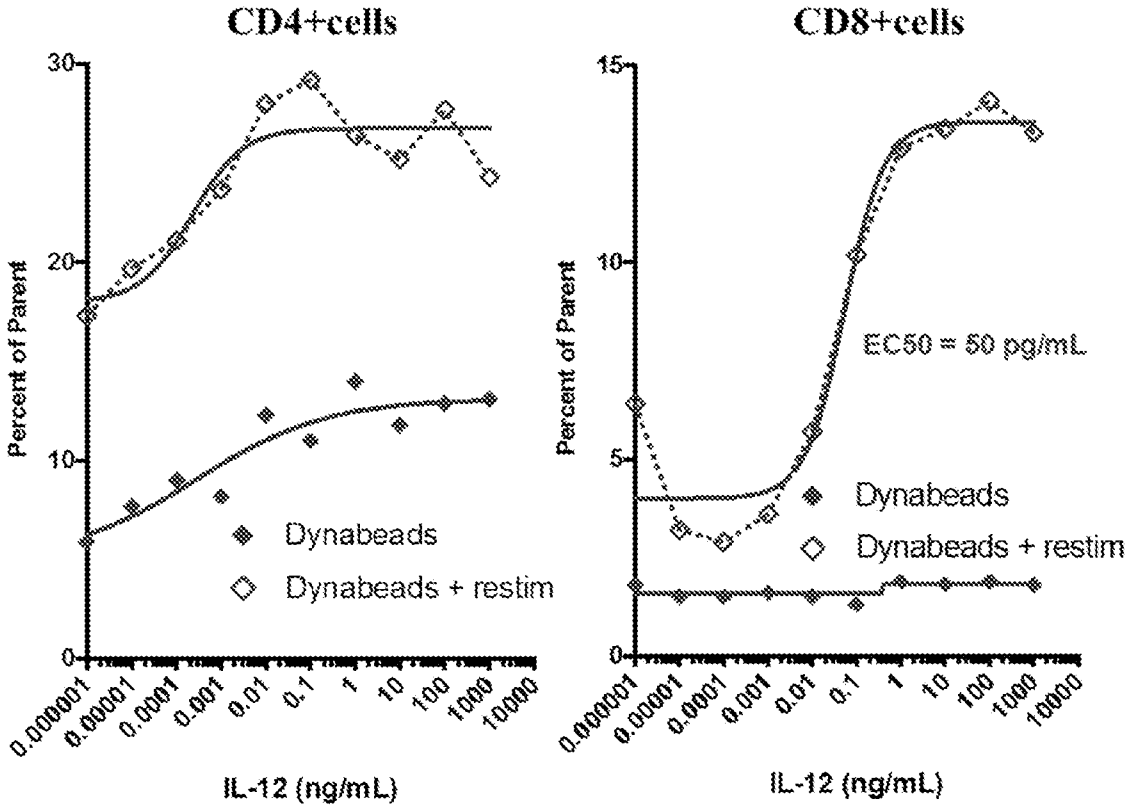

CD4+cells
Percent of Parent
30
20
10
0
Dynabeads
Dynabeads + restim
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
IL-12 (ng/mL)
CD8+cells
Percent of Parent
15
10
5
0
EC50 = 50 pg/mL
Dynabeads
Dynabeads + restim
0.000001
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
IL-12 (ng/mL)

Figure 28C

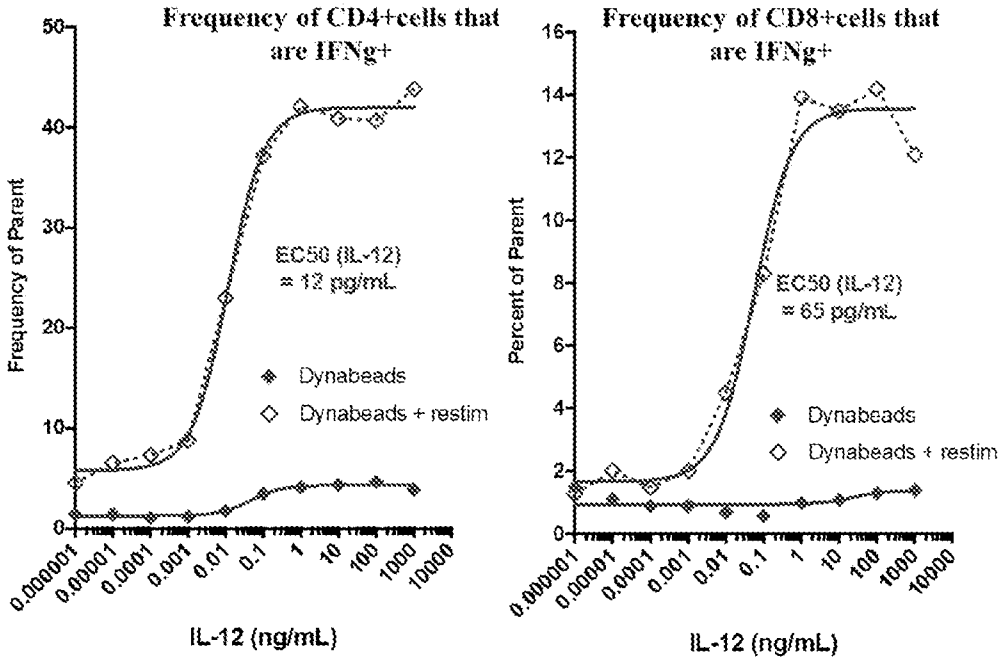


Figure 28D

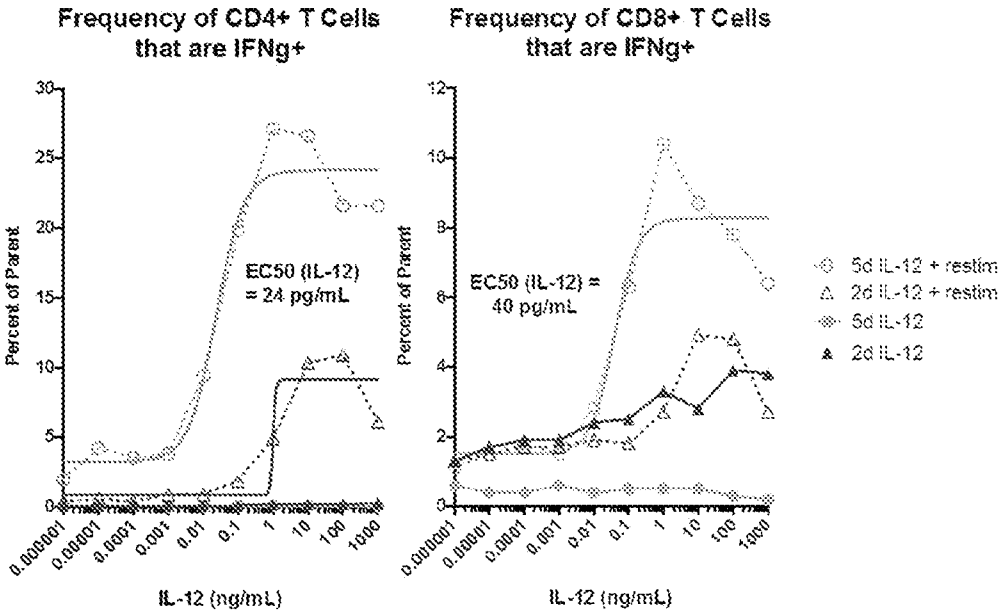


Figure 29

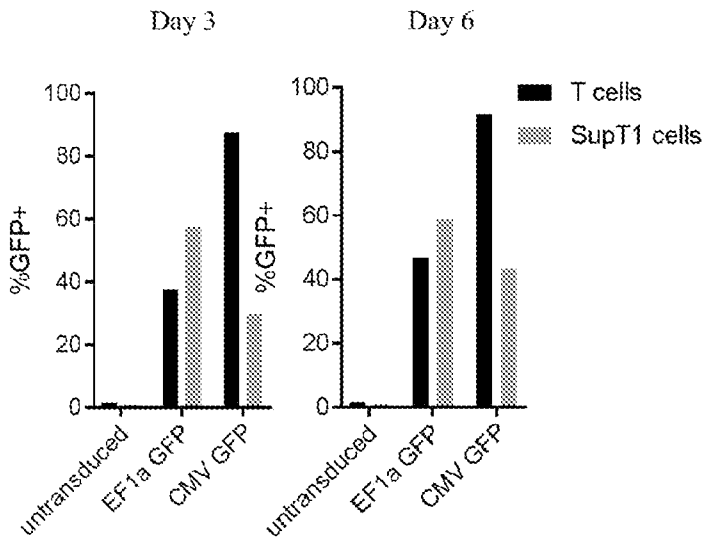

Day 3
Day 6
T cells
SupT1 cells
%GFP+
%GFP+
100
80
60
40
20
0
untransduced
EF1a GFP
CMV GFP

Figure 30A

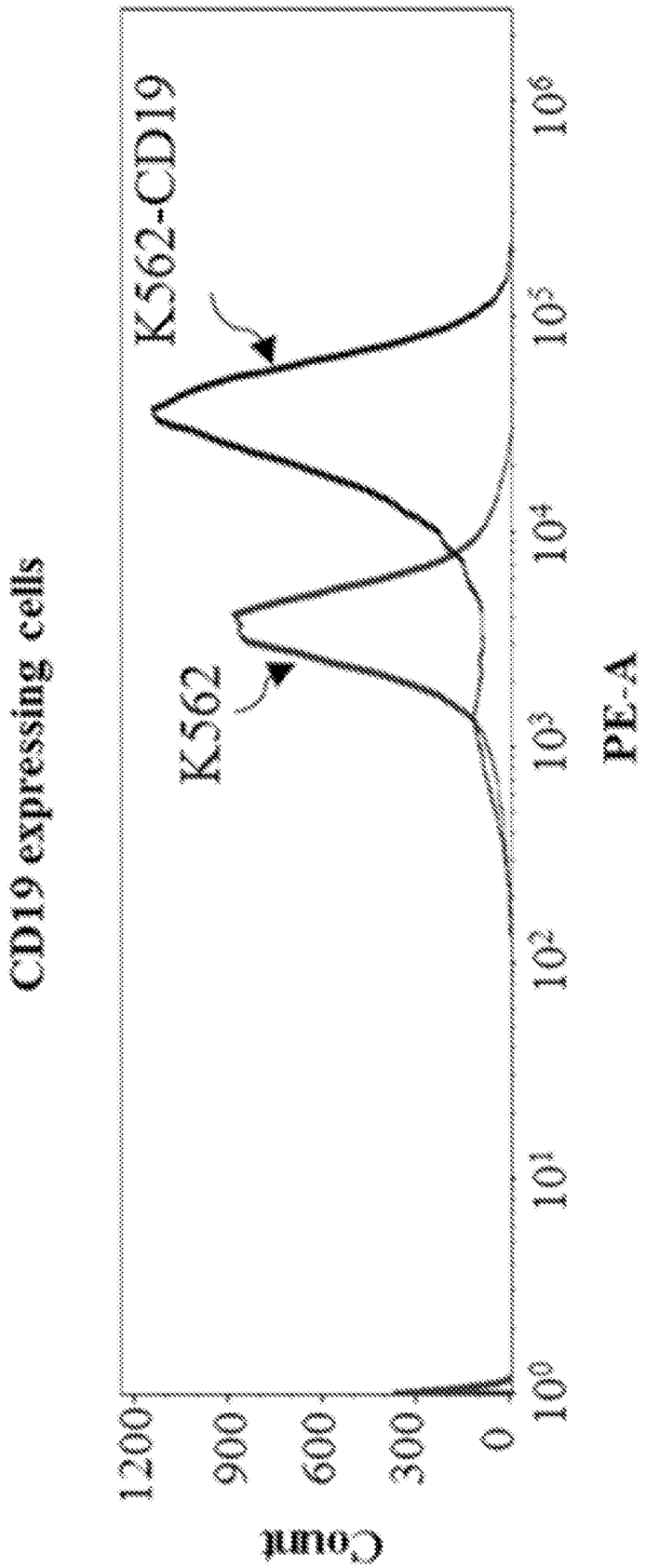

CD19 expressing cells
K562-CD19
K562
Count
PE-A
1200
900
600
300
0
10^0
10^1
10^2
10^3
10^4
10^5
10^6

Figure 30B

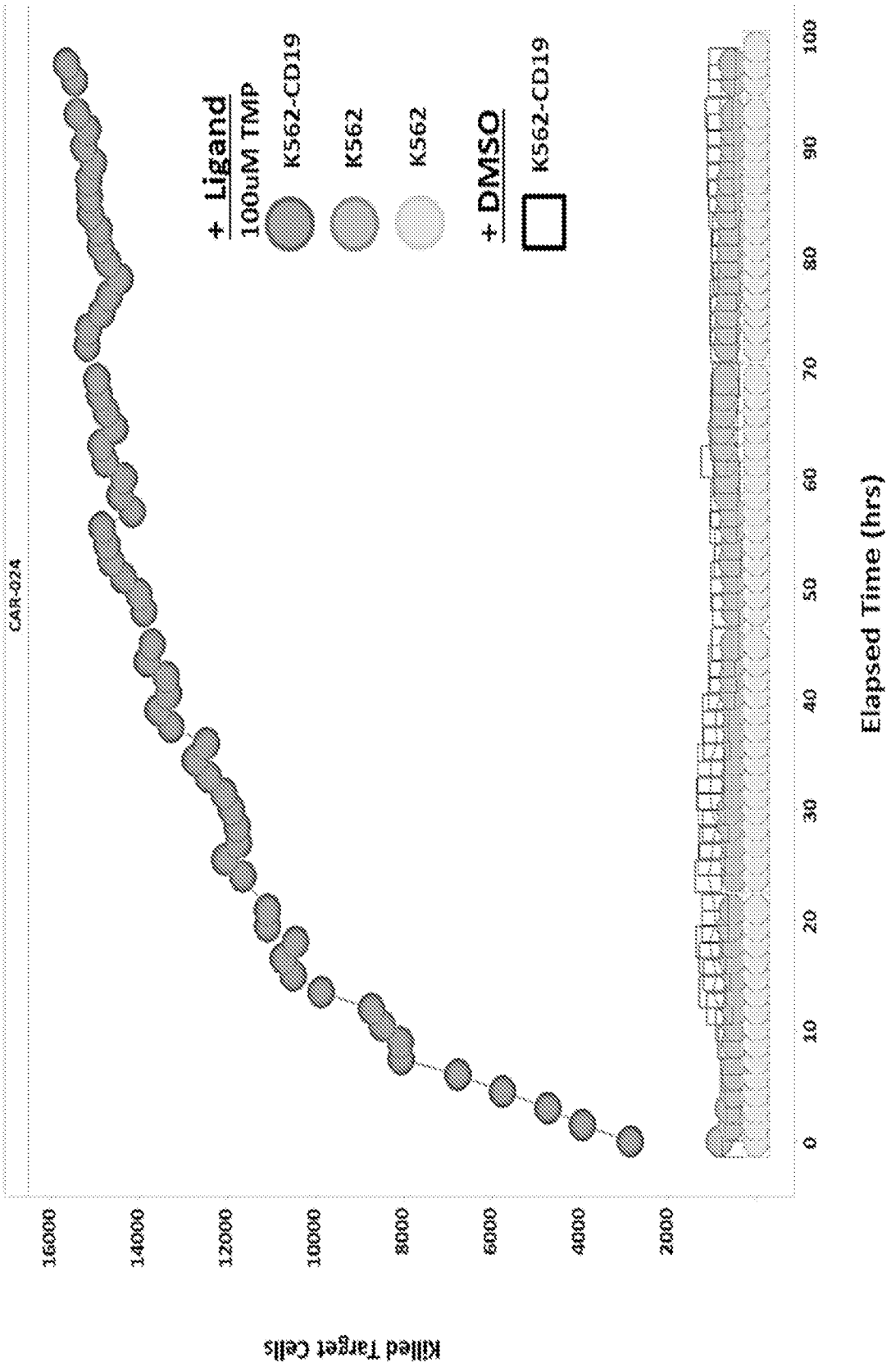

CAR-024
+ Ligand
100uM TMP
K562-CD19
K562
K562
+ DMSO
K562-CD19
Killed Target cells
16000
14000
12000
10000
8000
6000
4000
2000
0
10
20
30
40
50
60
70
80
90
100
Elapsed Time (hrs)

Figure 30C

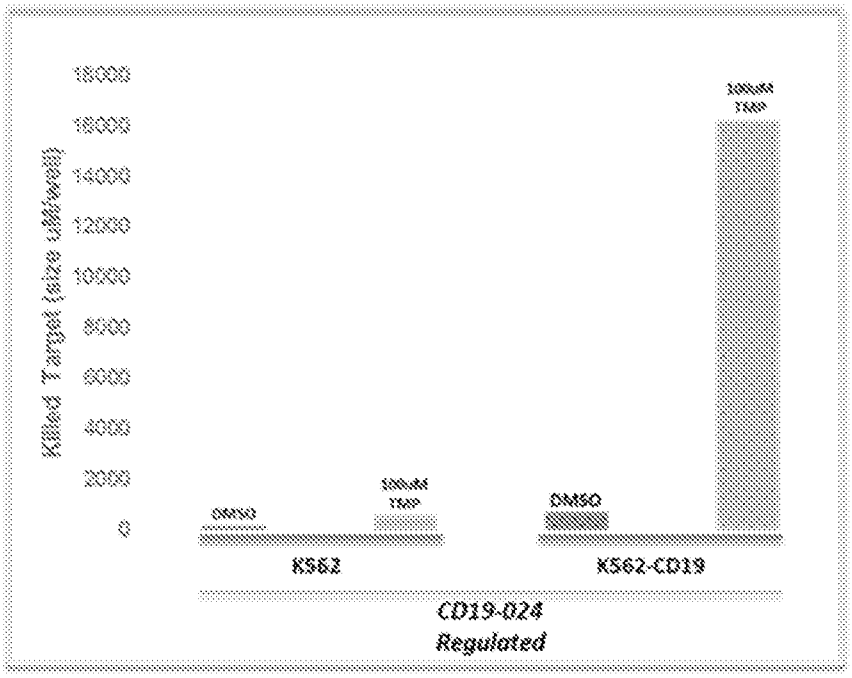

18000
16000
14000
12000
10000
8000
6000
4000
2000
0
K562 Target (size adjusted)
DMSO
100uM TMP
DMSO
100uM TMP
K562
K562-CD19
CD19-024
Regulated

Figure 31A

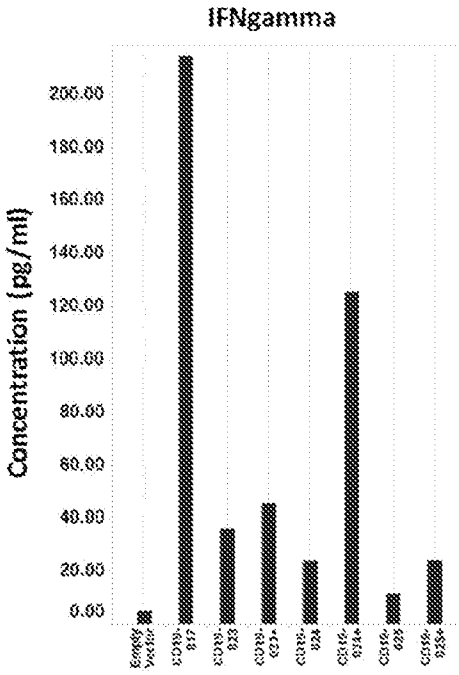


Figure 31B

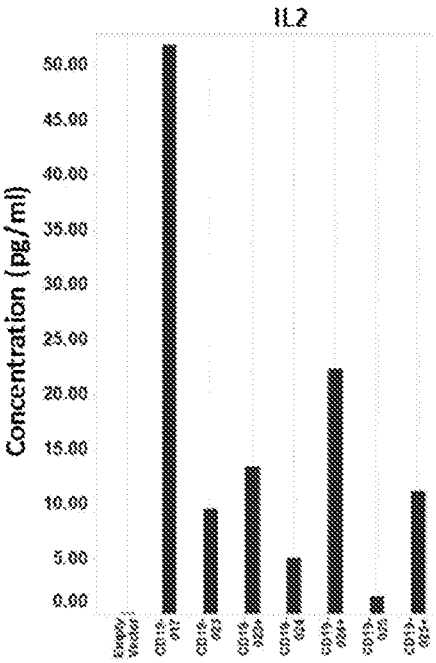


Figure 32A

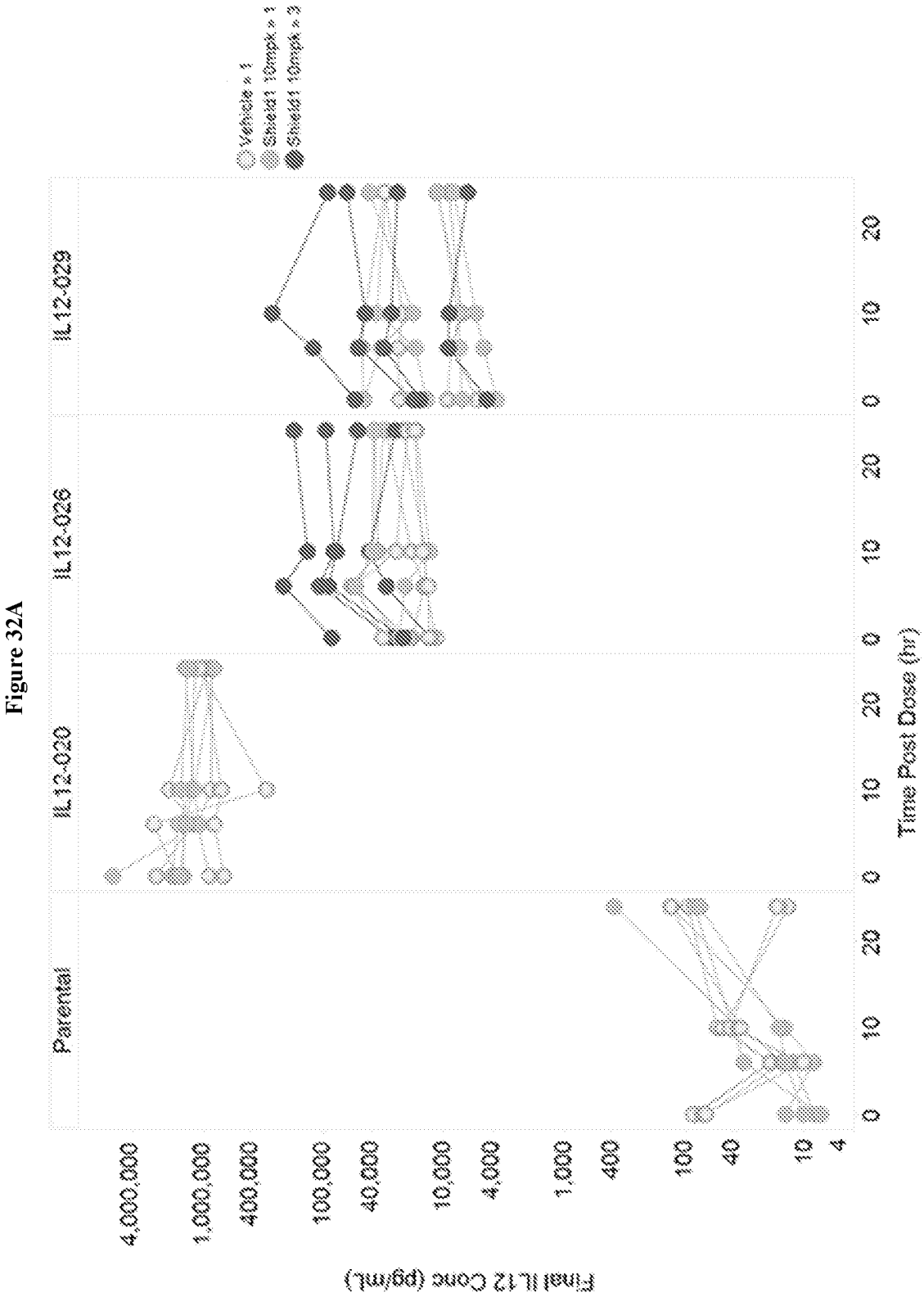

Vehicle × 1
Sheld1 10mpk × 1
Sheld1 10mpk × 3
Parental
IL12-020
IL12-026
IL12-029
Final IL12 Conc (pg/mL)
4,000,000
1,000,000
400,000
100,000
40,000
10,000
4,000
1,000
400
100
40
10
4
0
10
20
Time Post Dose (hr)

Figure 32B

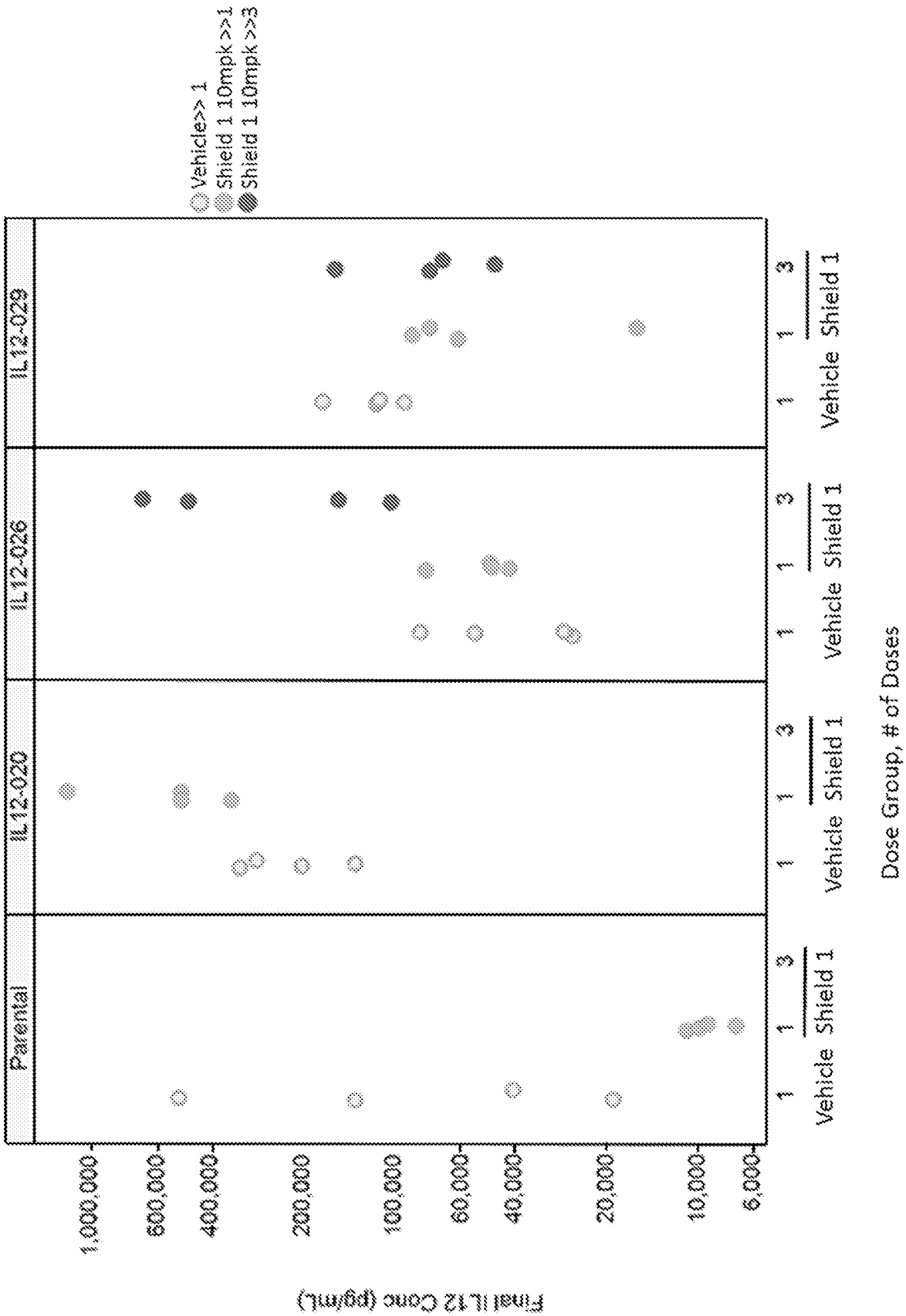
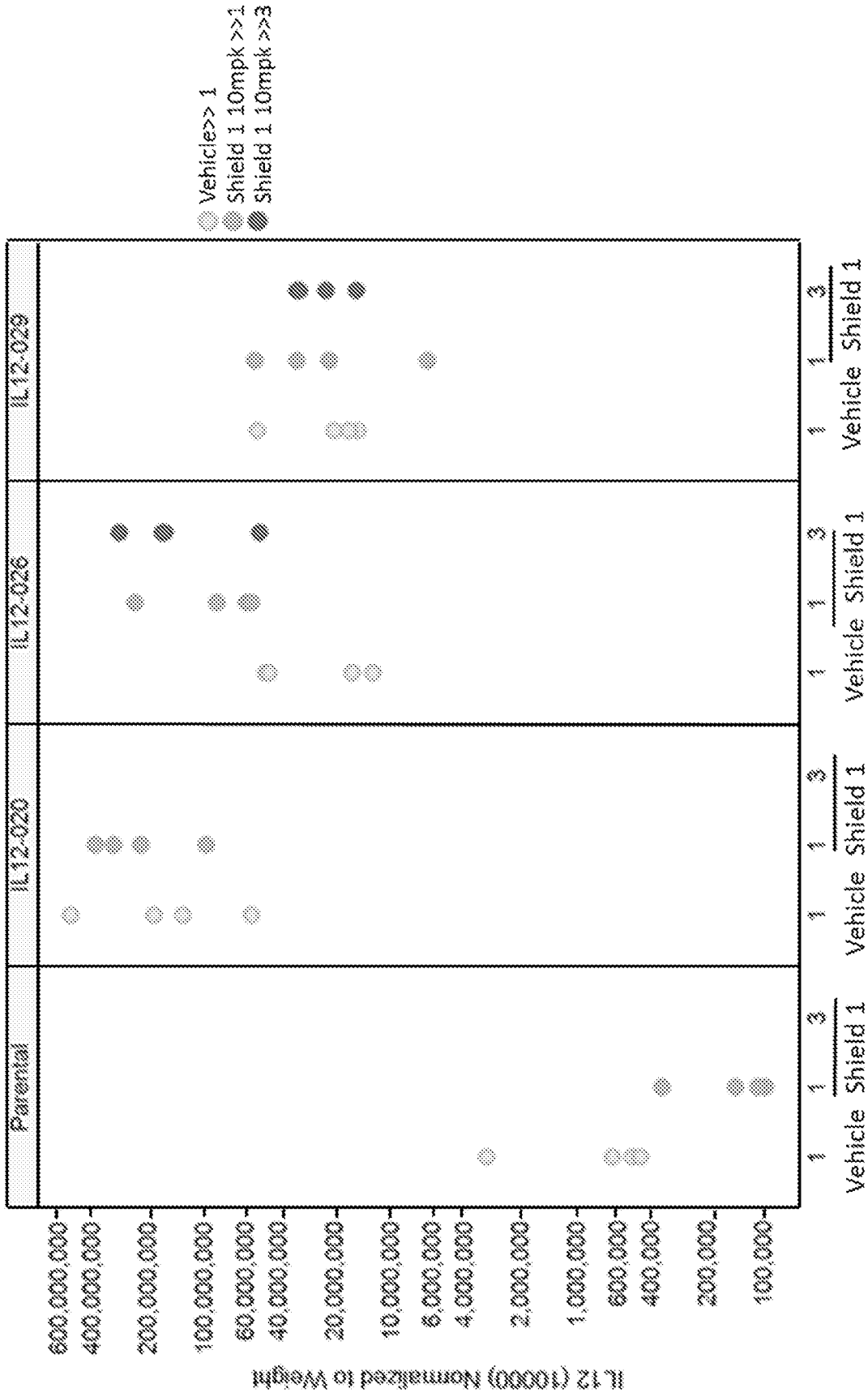

Vehicle>> 1
Shield 1 10mpk >>1
Shield 1 10mpk >>3
Parental
IL12-020
IL12-026
IL12-029
Final IL12 Conc (pg/mL)
1,000,000
600,000
400,000
200,000
100,000
60,000
40,000
20,000
10,000
6,000
1 1 3
Vehicle Shield 1
Dose Group, # of Doses

Figure 32C


Vehicle>> 1
Shield 1 10mpk >>1
Shield 1 10mpk >>3
Parental
IL12-020
IL12-026
IL12-029
IL-12 (10000) Normalized to Weight
600,000,000
400,000,000
200,000,000
100,000,000
60,000,000
40,000,000
20,000,000
10,000,000
6,000,000
4,000,000
2,000,000
1,000,000
600,000
400,000
200,000
100,000
1 1 3
Vehicle Shield 1
Dose Group, # of Doses

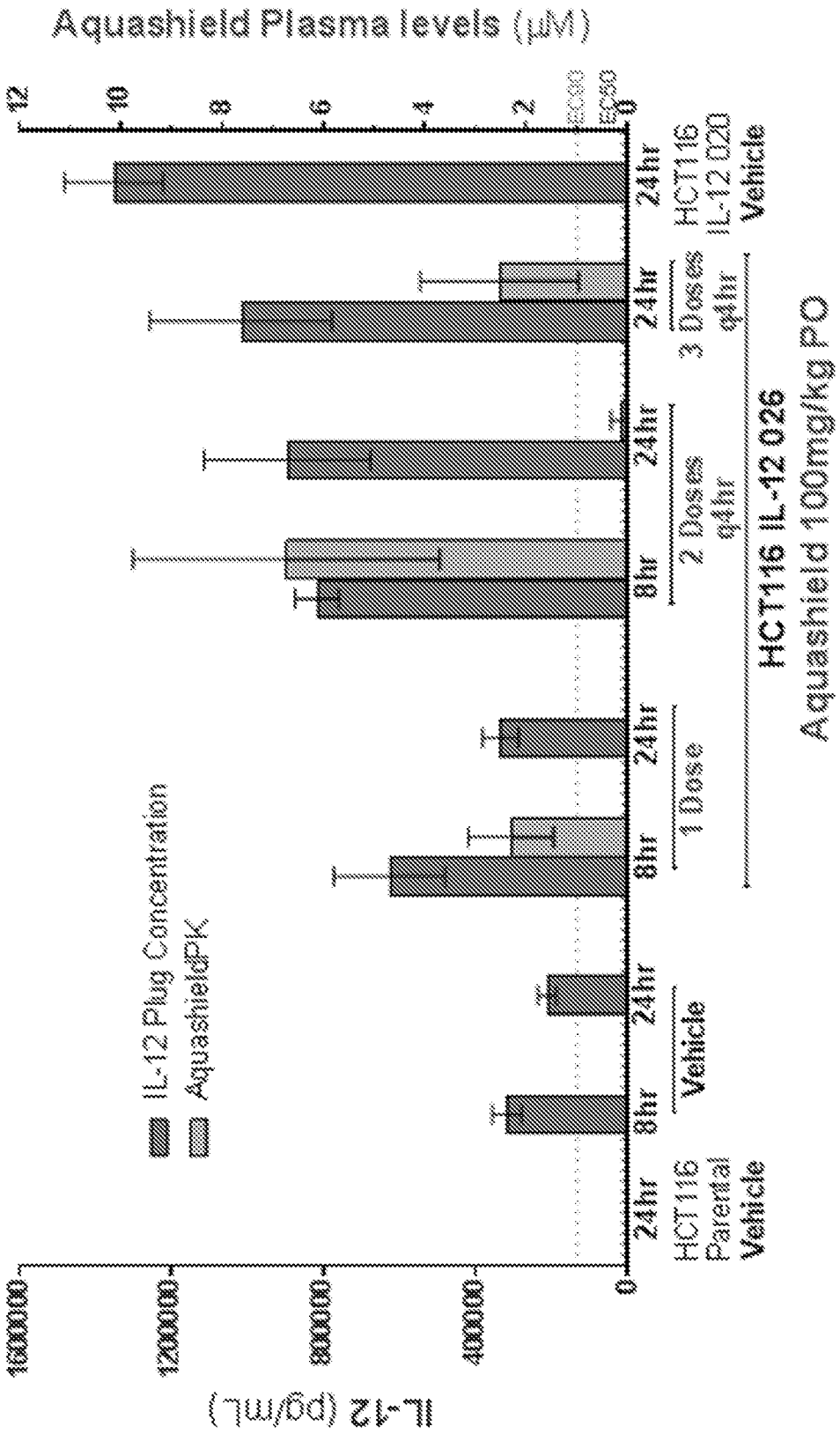

Aquashield Plasma levels (μM)
12
10
8
6
4
2
0
EC90
EC50
IL-12 Plug Concentration
AquashieldPK
IL-12 (pg/mL)
1600000
1200000
800000
400000
0
24hr
8hr
24hr
HCT116 Parental
Vehicle
1 Dose
Vehicle
2 Doses
q4hr
3 Doses
q4hr
HCT116 IL-12 020
Vehicle
HCT116 IL-12 026
Aquashield 100mg/kg PO

Figure 33A

Figure 33B

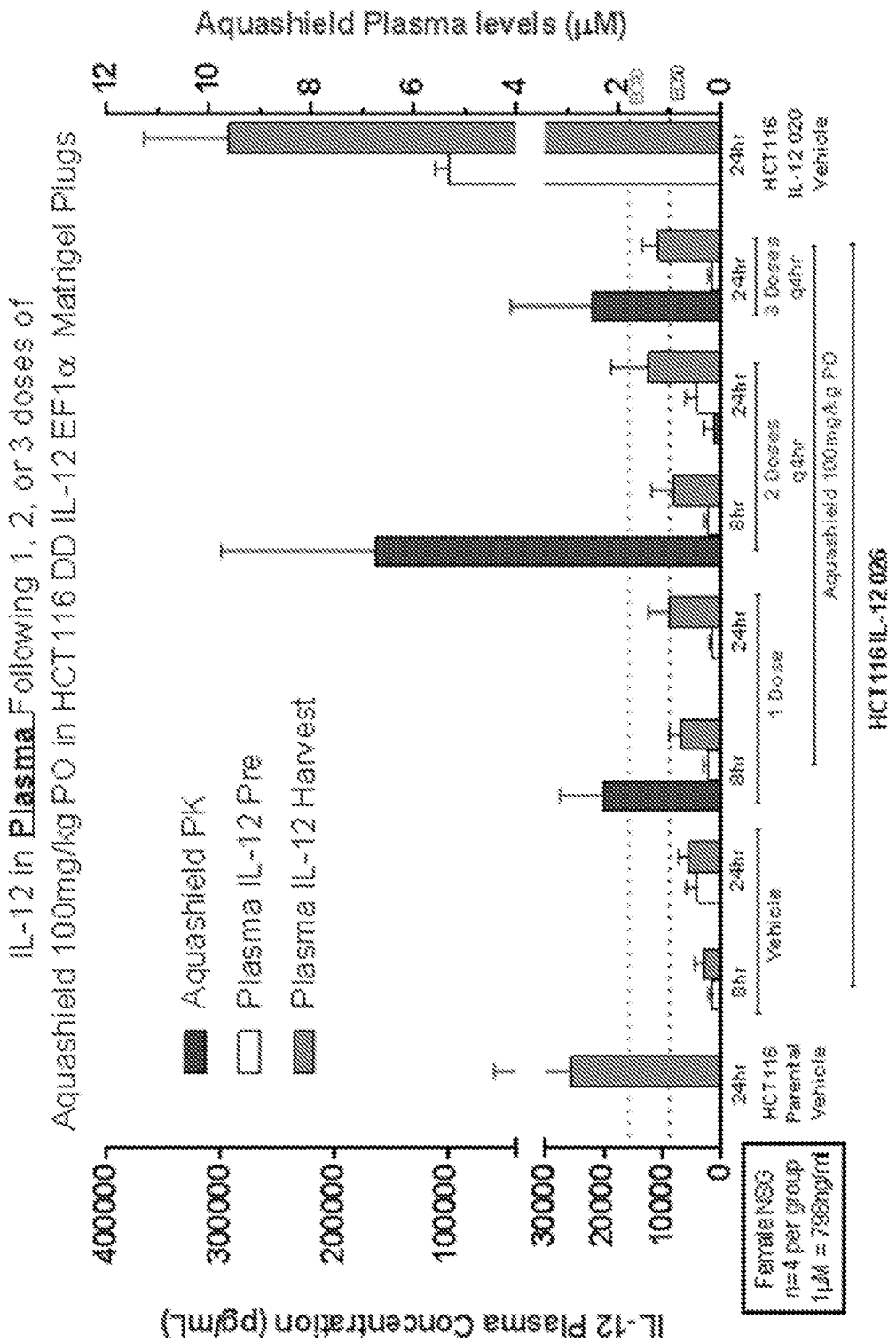

IL-12 in Plasma Following 1, 2, or 3 doses of
Aquashield 100mg/kg PO in HCT116 DD IL-12 EF1α Matrigel Plugs
Aquashield PK
Plasma IL-12 Pre
Plasma IL-12 Harvest
Aquashield Plasma levels (µM)
IL-12 Plasma Concentration (pg/mL)
Female NSG
n=4 per group
1µM = 786ng/ml
HCT116 Parental Vehicle
HCT116 IL-12 020 Vehicle
Vehicle
1 Dose
2 Doses q4hr
3 Doses q4hr
Aquashield 100mg/kg PO
HCT116 IL-12 026
8hr
24hr

Figure 33C

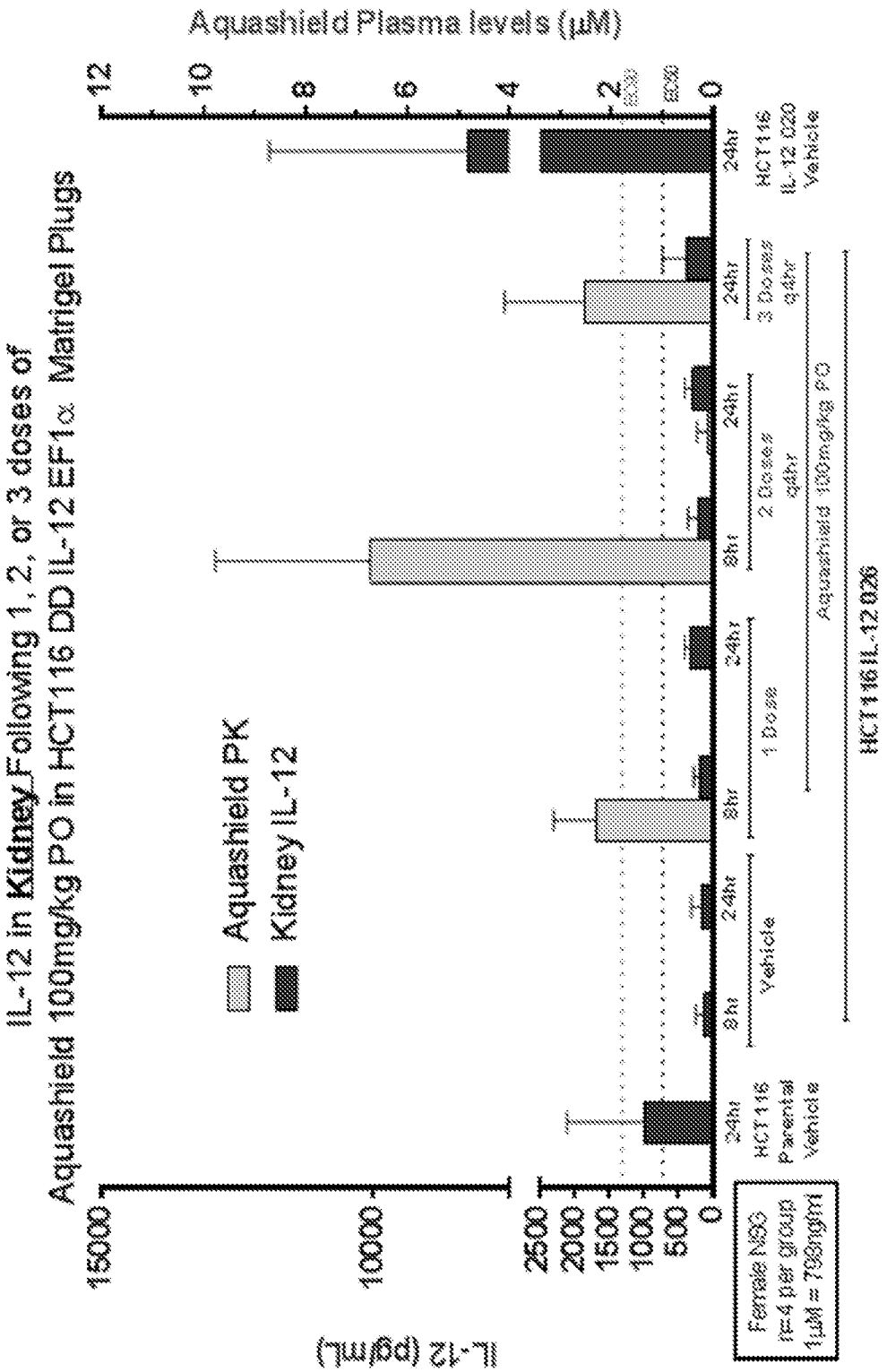

IL-12 in Kidney Following 1, 2, or 3 doses of
Aquashield 100mg/kg PO in HCT116 DD IL-12 EF1α Matrigel Plugs
Aquashield Plasma levels (μM)
IL-12 (pg/mL)
Aquashield PK
Kidney IL-12
Female NSG
n=4 per group
1μM = 798ng/ml
HCT116 Parental Vehicle
HCT116 IL-12 026
Vehicle
1 Dose
2 Doses
3 Doses
q8hr
Aquashield 100mg/kg PO
HCT116 IL-12 026
Vehicle

Figure 34A

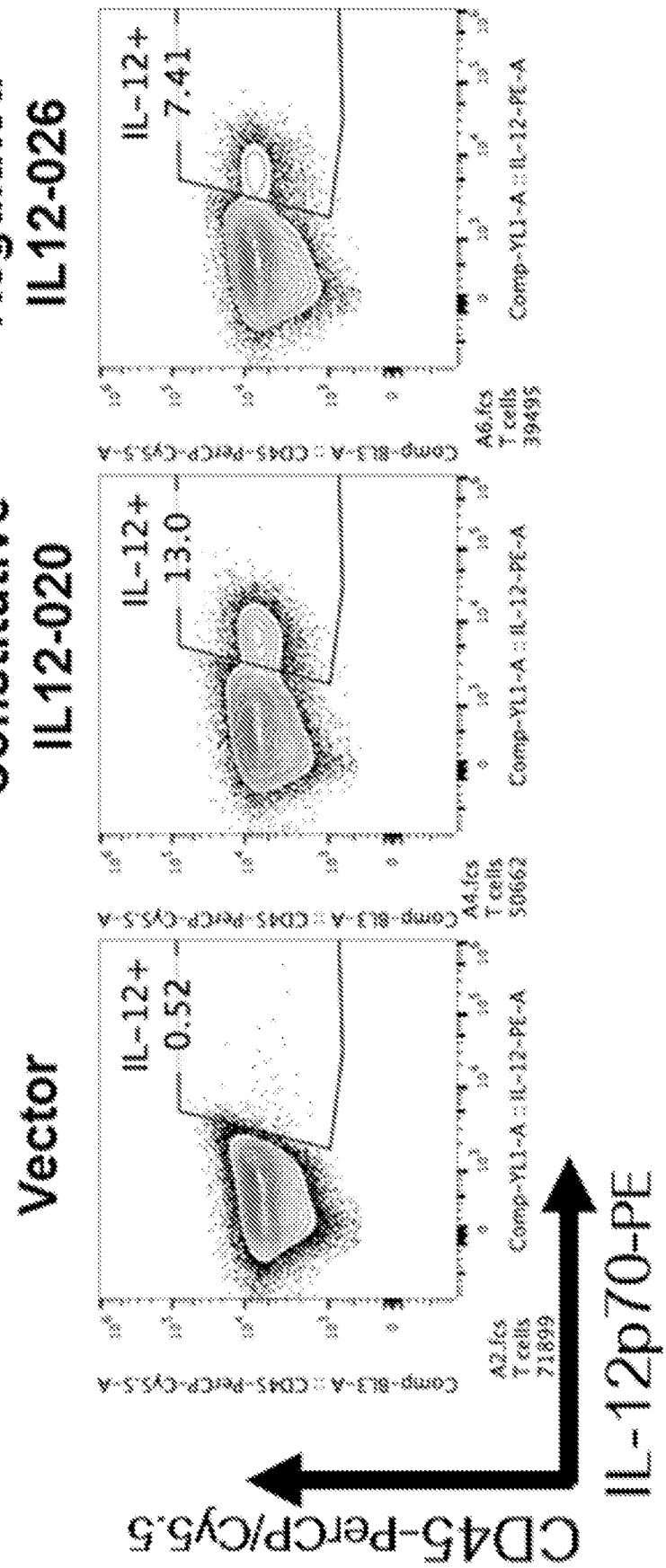

Vector
Constitutive IL12-020
Regulated IL12-026
IL-12+ 0.52
IL-12+ 13.0
IL-12+ 7.41
A2.fcs T cells 21899
A4.fcs T cells 50662
A6.fcs T cells 39495
CD45-PerCP/Cy5.5
IL-12p70-PE

Figure 34B

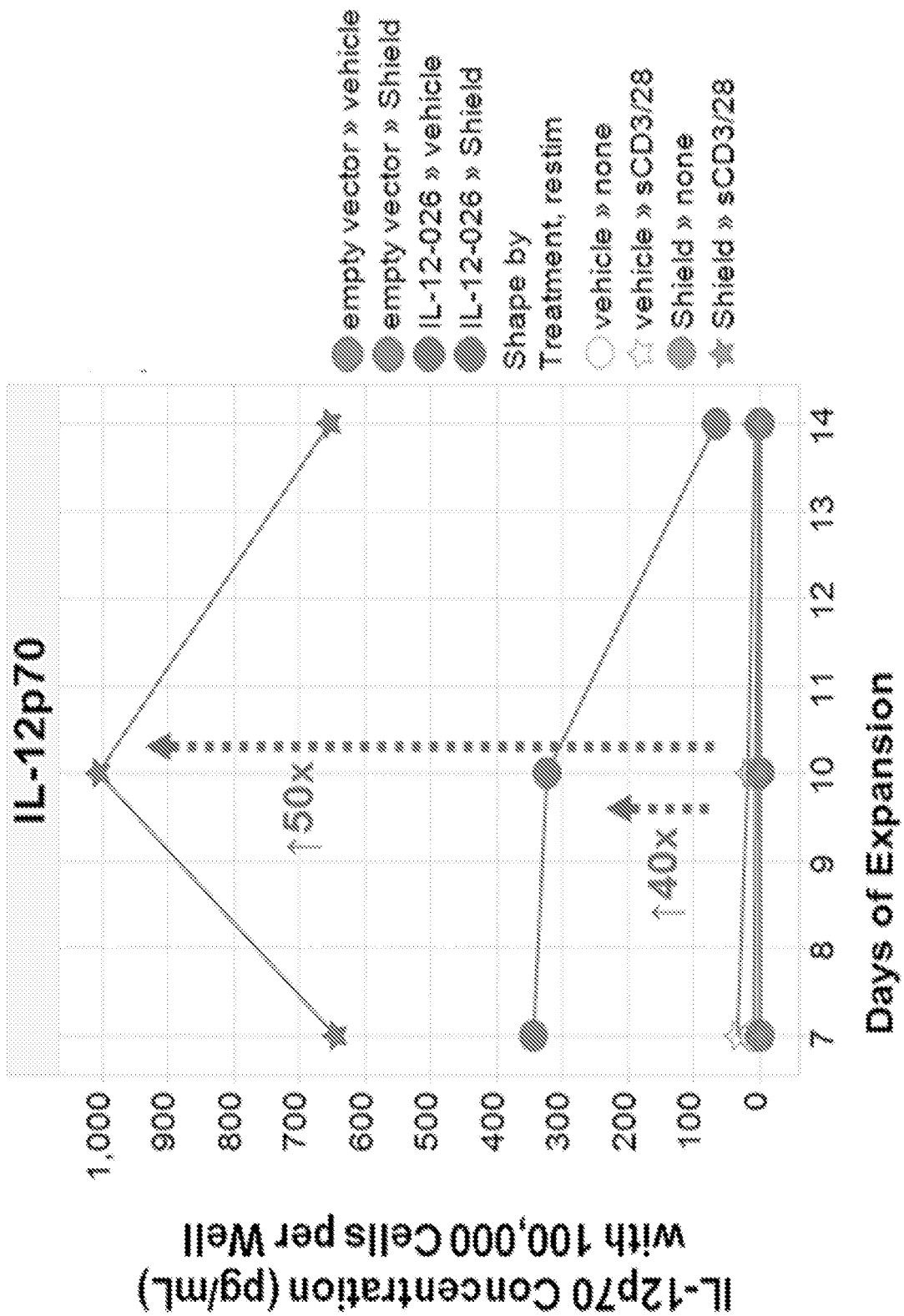

IL-12p70
IL-12p70 Concentration (pg/mL) with 100,000 Cells per Well
1,000
900
800
700
600
500
400
300
200
100
0
7
8
9
10
11
12
13
14
Days of Expansion
↑50x
↑40x
empty vector » vehicle
empty vector » Shield
IL-12-026 » vehicle
IL-12-026 » Shield
Shape by
Treatment, restim
vehicle » none
vehicle » sCD3/28
Shield » none
Shield » sCD3/28

Figure 34C

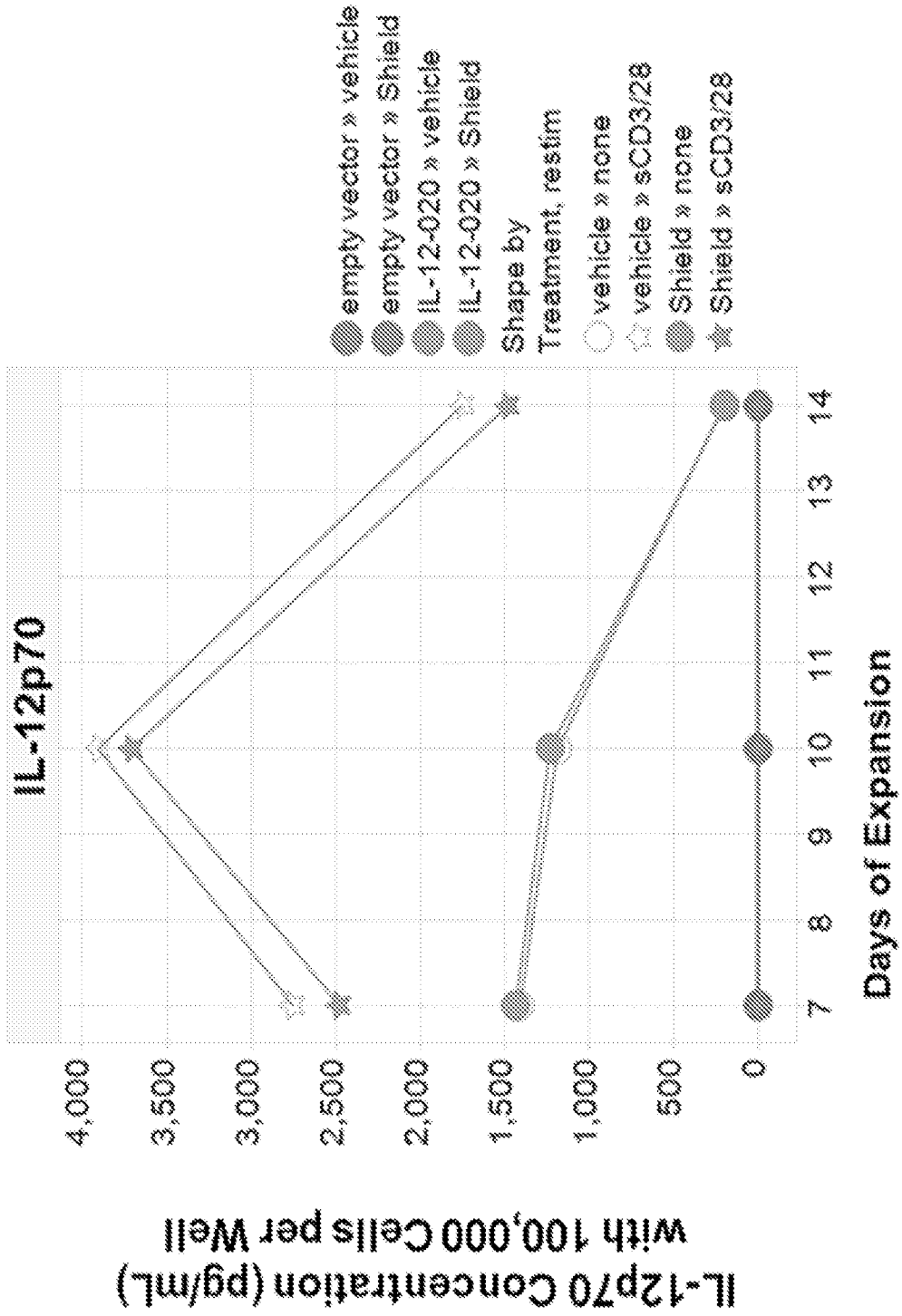

IL-12p70
IL-12p70 Concentration (pg/mL) with 100,000 Cells per Well
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
7
8
9
10
11
12
13
14
Days of Expansion
empty vector » vehicle
empty vector » Shield
IL-12-020 » vehicle
IL-12-020 » Shield
Shape by
Treatment, restim
vehicle » none
vehicle » sCD3/28
Shield » none
Shield » sCD3/28

Figure 35A

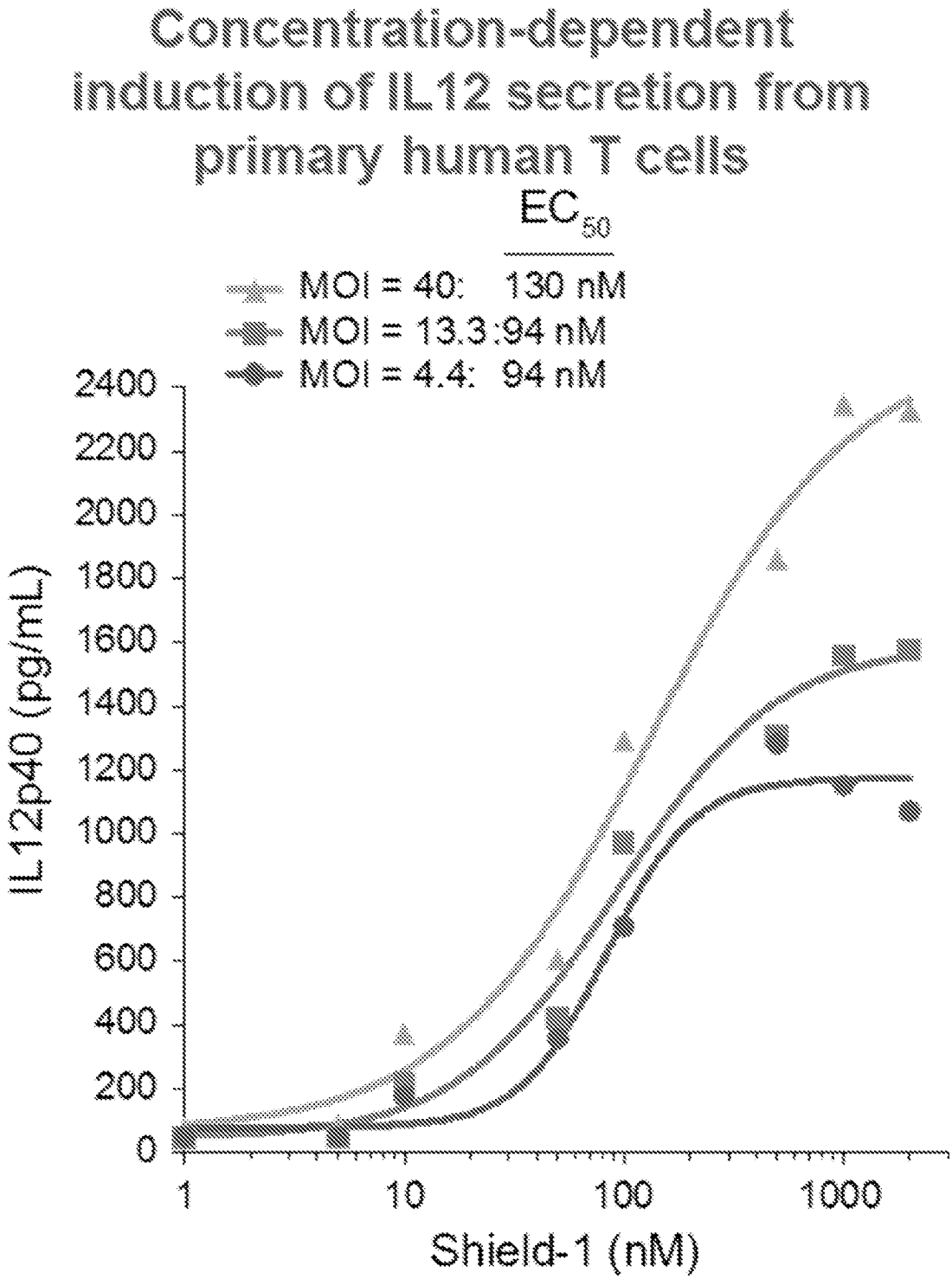

Concentration-dependent induction of IL12 secretion from primary human T cells
EC50
MOI = 40: 130 nM
MOI = 13.3 :94 nM
MOI = 4.4: 94 nM
IL12p40 (pg/mL)
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1
10
100
1000
Shield-1 (nM)

Figure 35B

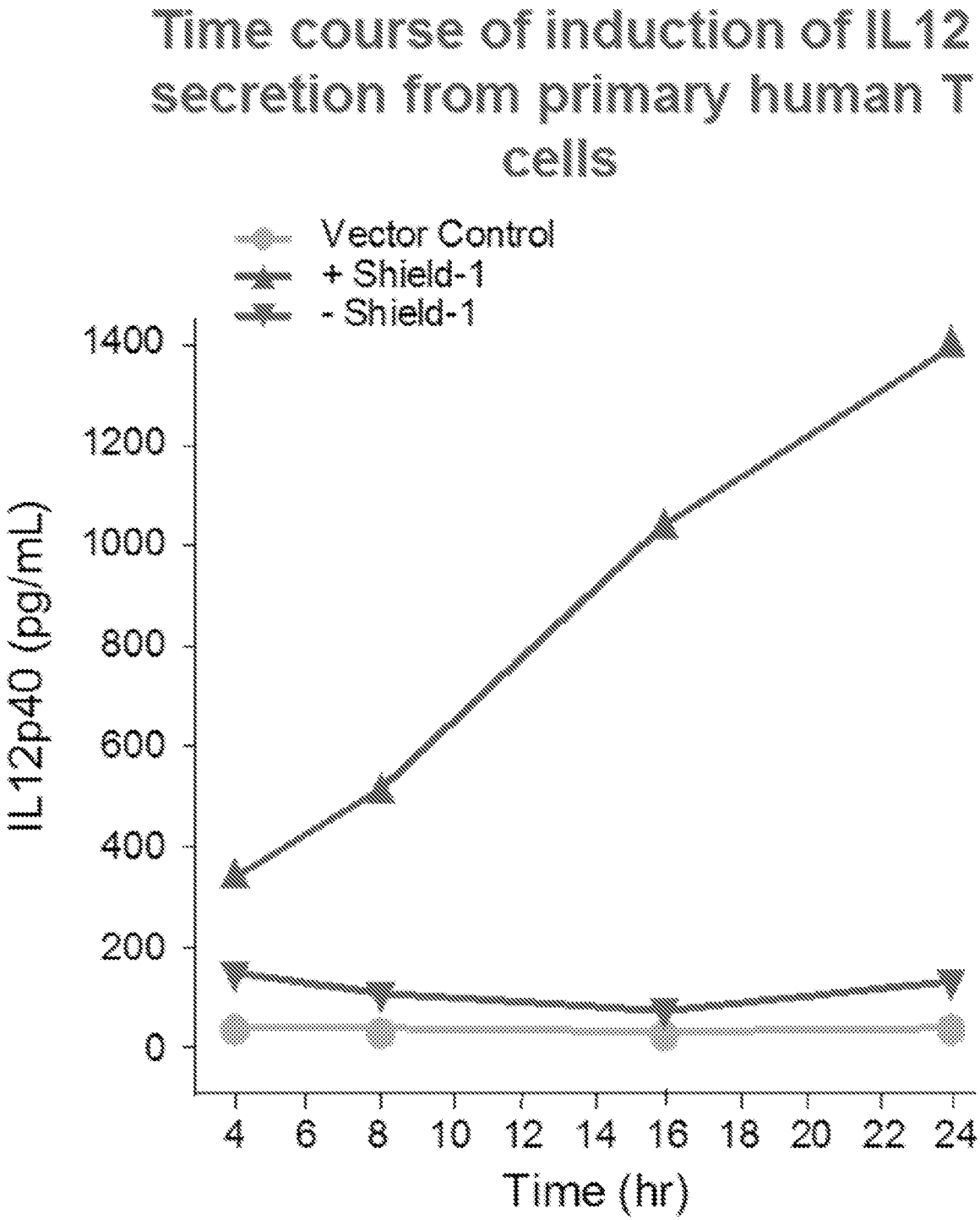

Time course of induction of IL12 secretion from primary human T cells
Vector Control
+ Shield-1
- Shield-1
IL12p40 (pg/mL)
1400
1200
1000
800
600
400
200
0
4
6
8
10
12
14
16
18
20
22
24
Time (hr)

Figure 36A

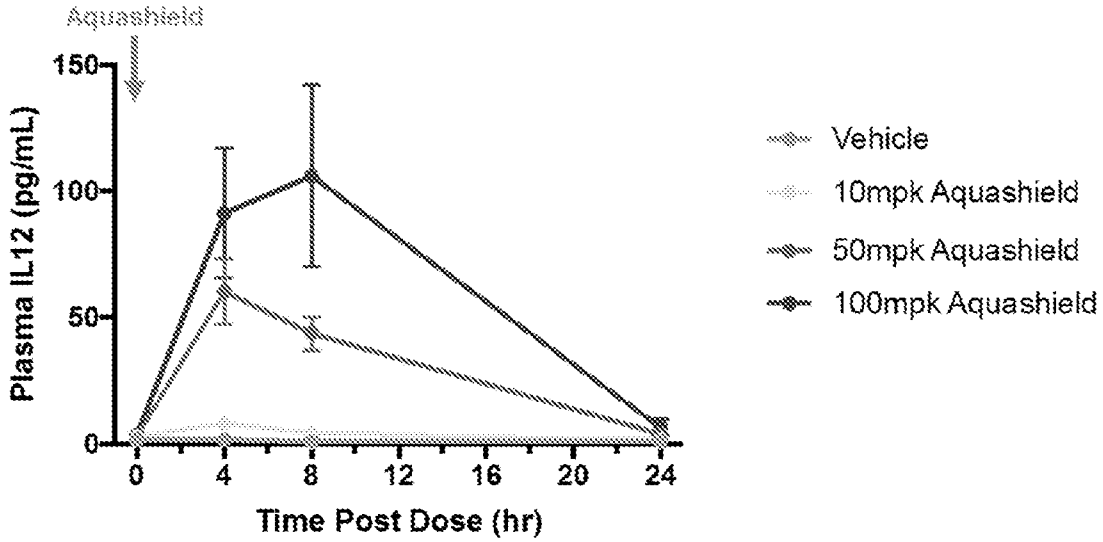


Figure 36B

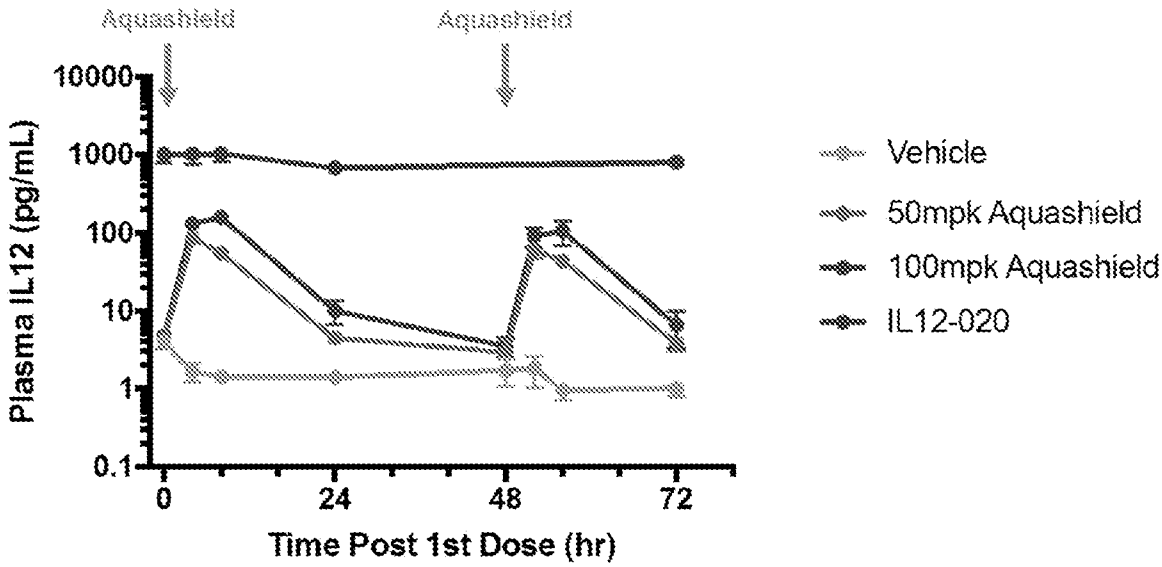


Figure 37A

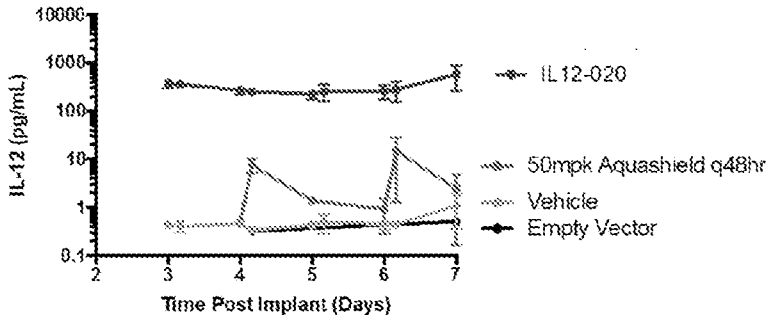


Figure 37B

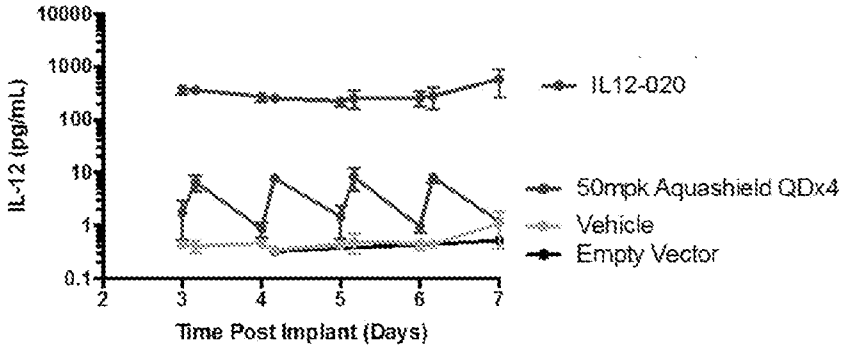


Figure 37C

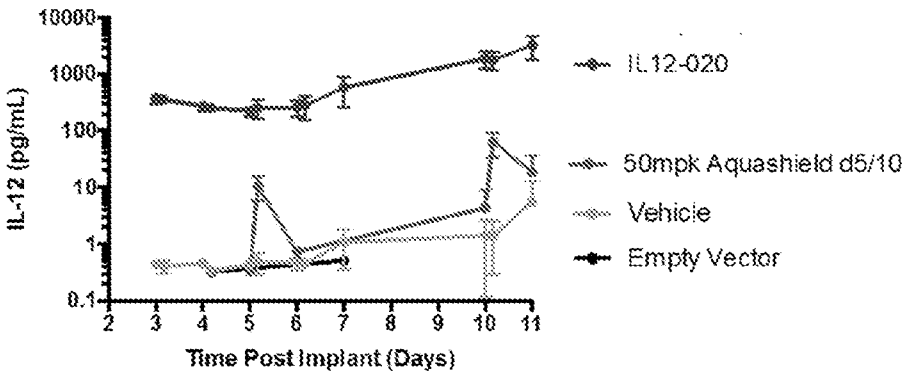


Figure 37D

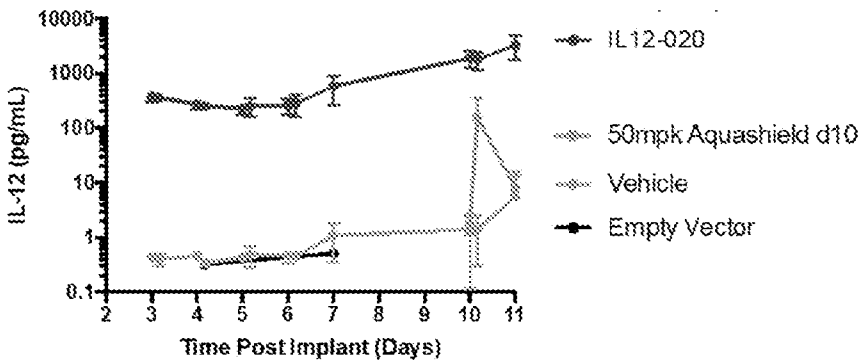


Figure 37E

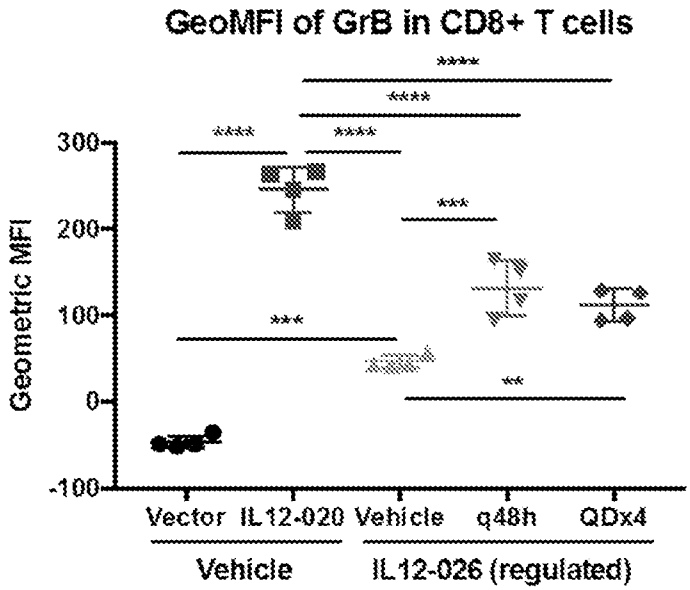


Figure 37F

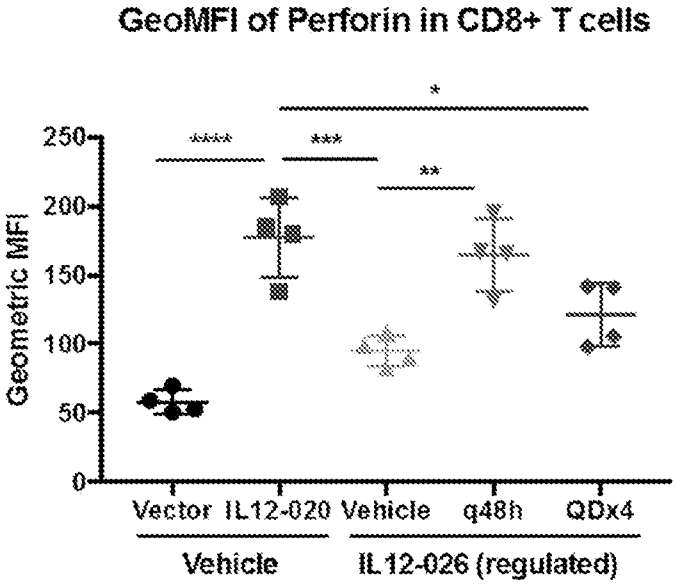


Figure 38A

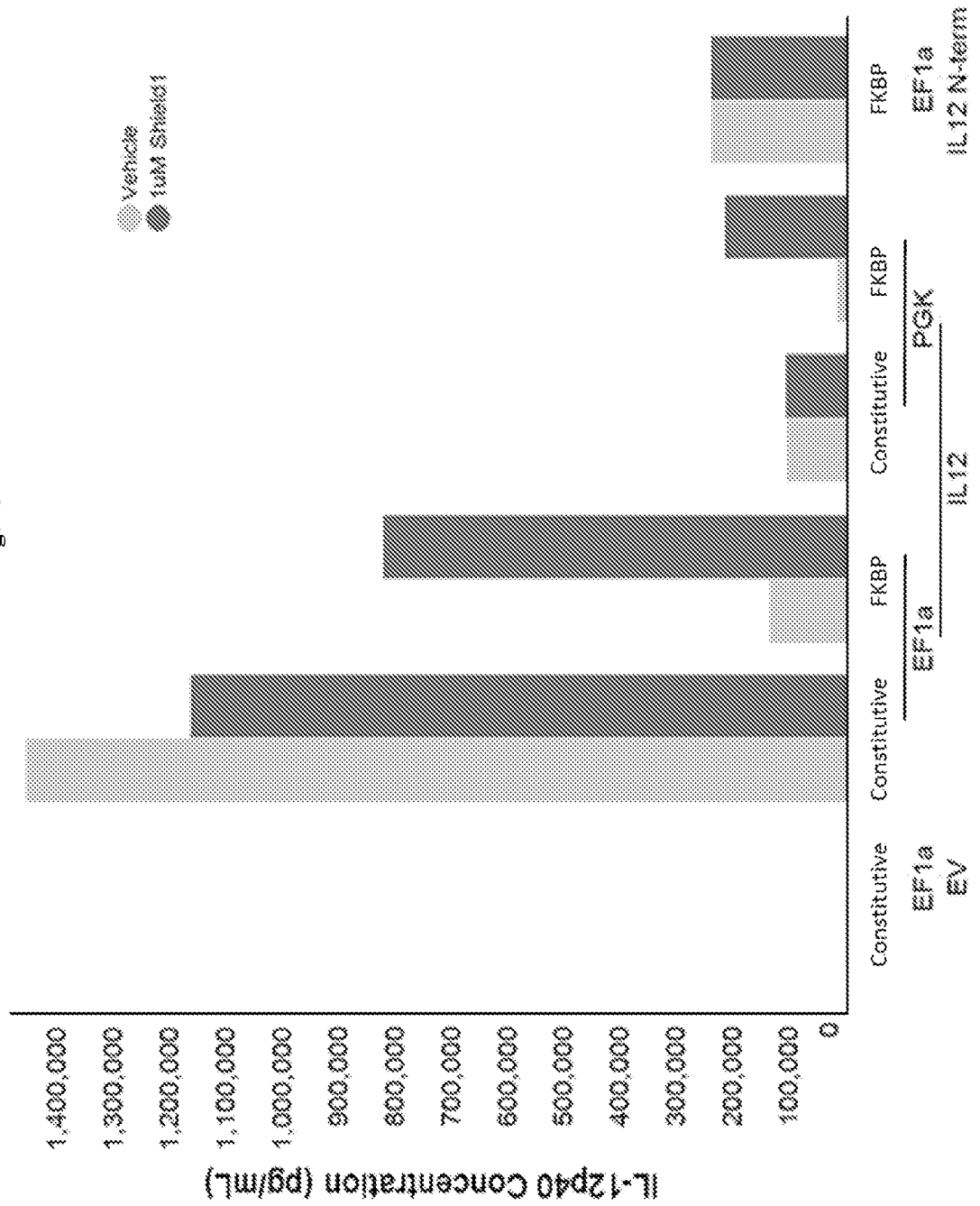

Vehicle
1uM Shield1
IL-12p40 Concentration (pg/mL)
1,400,000
1,300,000
1,200,000
1,100,000
1,000,000
900,000
800,000
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0
Constitutive
EF1a
EV
Constitutive
FKBP
EF1a
IL12
Constitutive
FKBP
PGK
FKBP
EF1a
IL12 N-term

Figure 38B

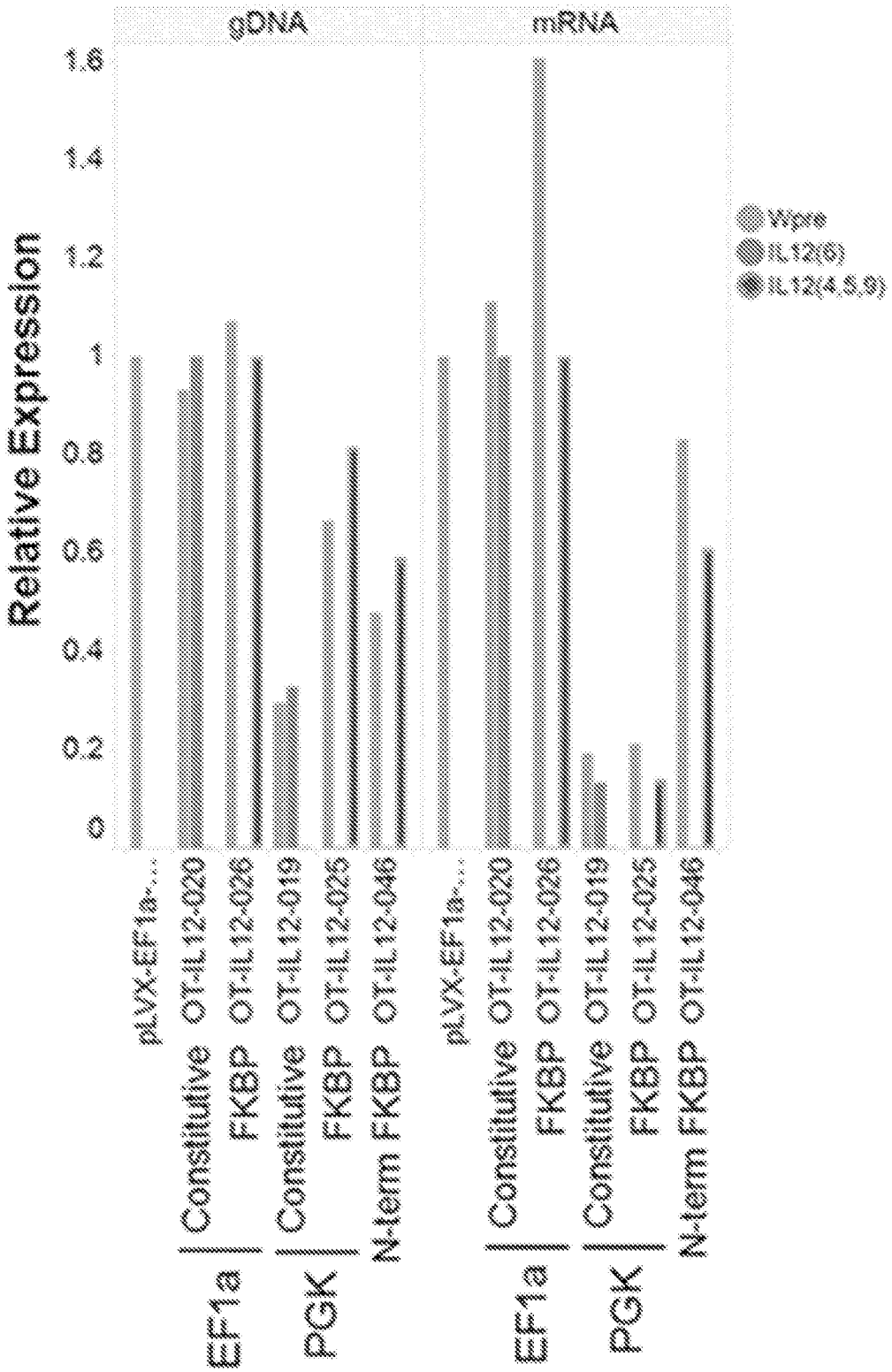

gDNA
mRNA
Relative Expression
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Wpre
IL12(p)
IL12(4.5.9)
pLVX-EF1a-...
OT-IL12-020
OT-IL12-026
OT-IL12-019
OT-IL12-025
OT-IL12-046
EF1a
PGK
Constitutive
FKBP
N-term FKBP

Figure 39

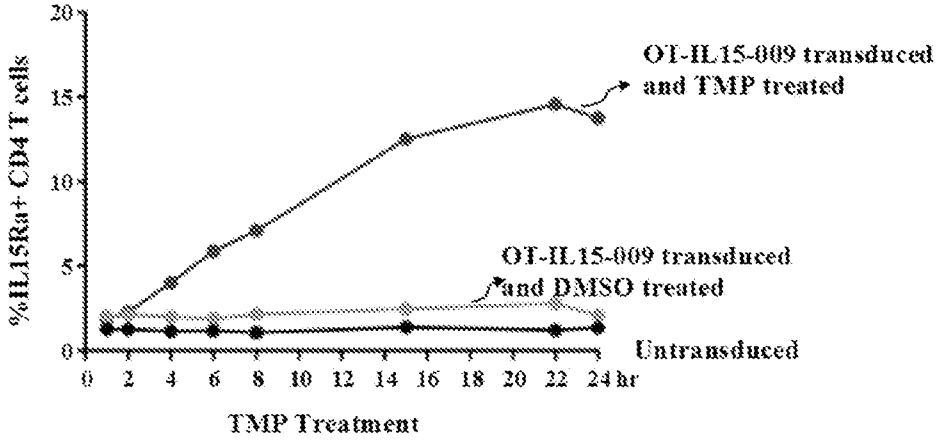


Figure 40

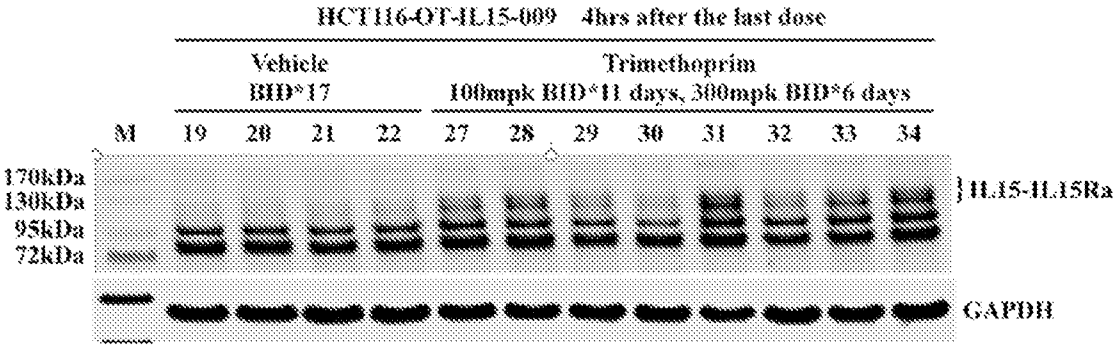


Figure 41

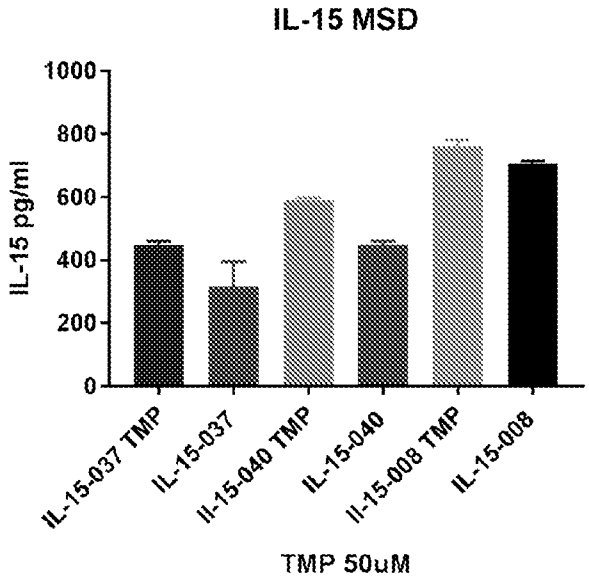
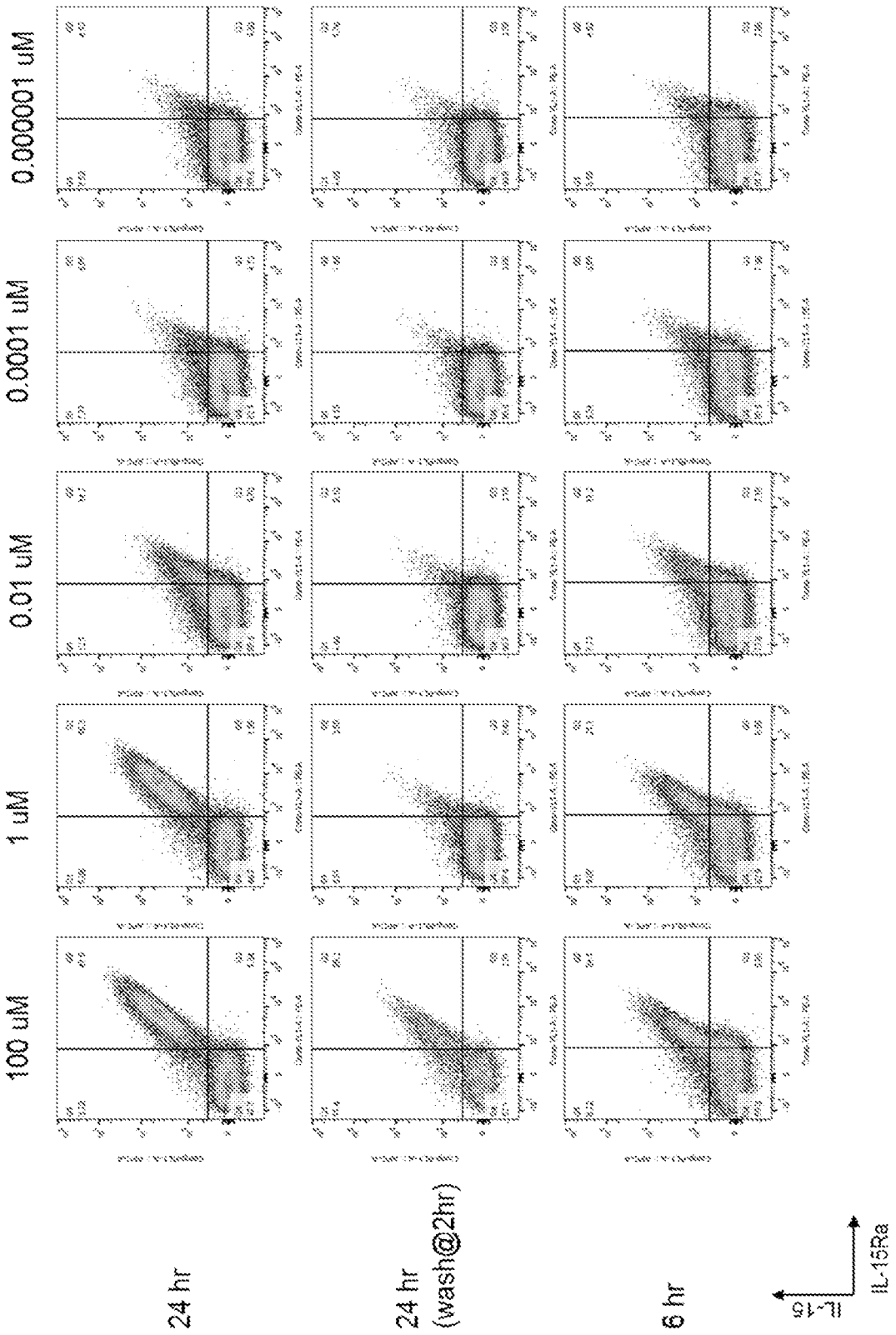


Figure 42A


100 uM
1 uM
0.01 uM
0.0001 uM
0.000001 uM
24 hr
24 hr (wash@2hr)
6 hr
IL-15
IL-15Ra

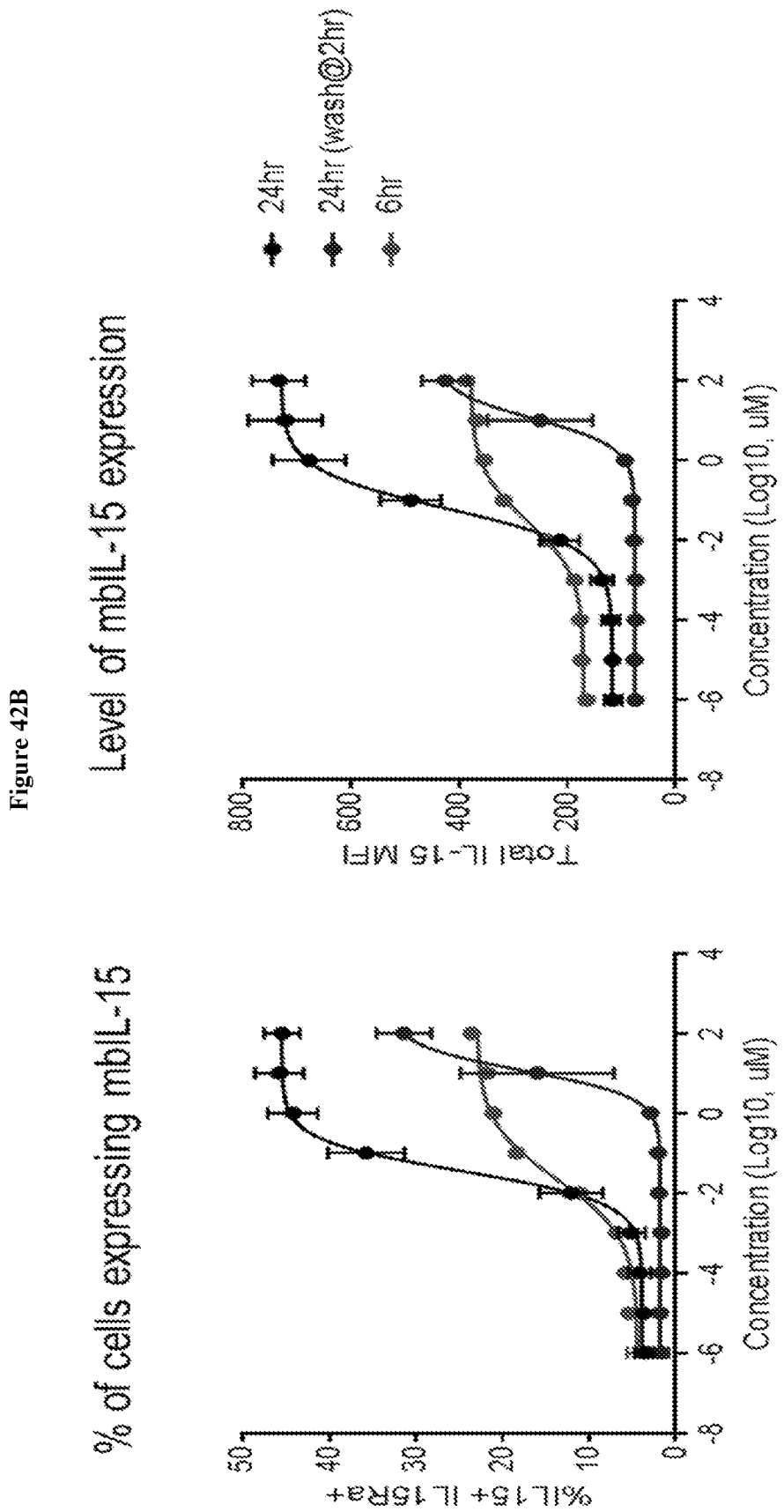

Level of mbIL-15 expression
24hr
24hr (wash@2hr)
6hr
Total IL-15 MFI
800
600
400
200
0
-8
-6
-4
-2
0
2
4
Concentration (Log10, uM)
% of cells expressing mbIL-15
%IL15+ IL15Ra+
50
40
30
20
10
0
-8
-6
-4
-2
0
2
4
Concentration (Log10, uM)

Figure 42B

Figure 43A

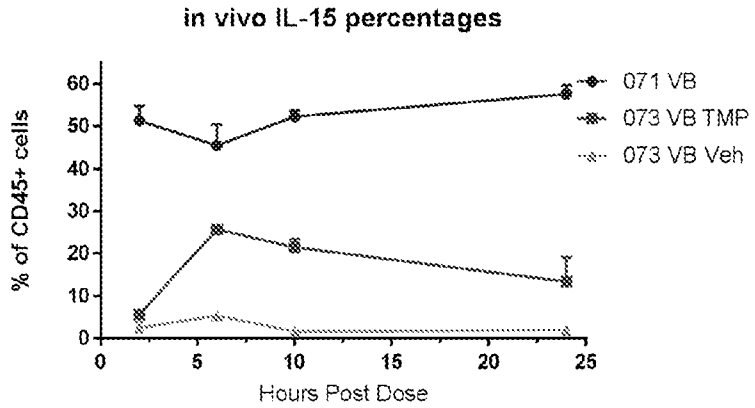


Figure 43B

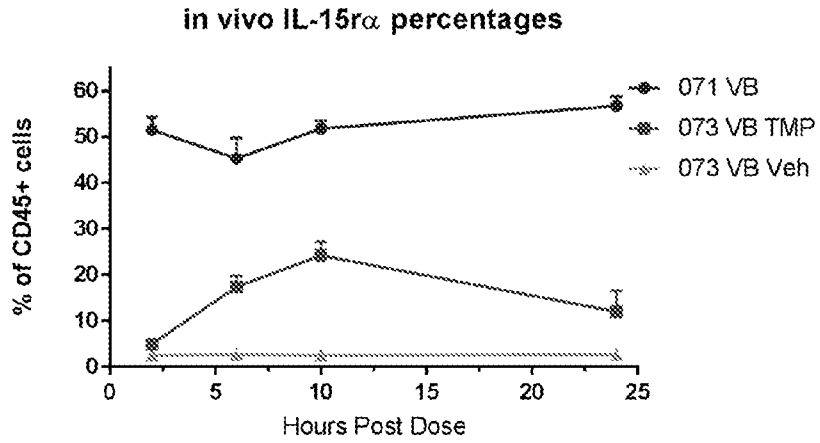


Figure 43C

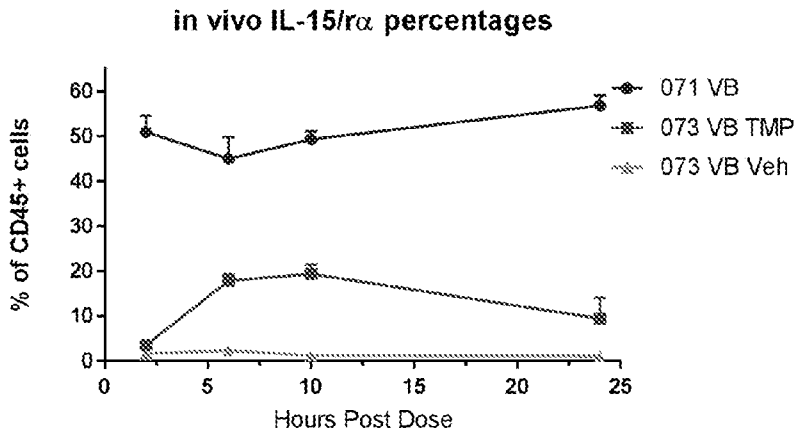

in vivo IL-15/rα percentages
% of CD45+ cells
60
50
40
30
20
10
0
0
5
10
15
20
25
Hours Post Dose
071 VB
073 VB TMP
073 VB Veh

Figure 43D

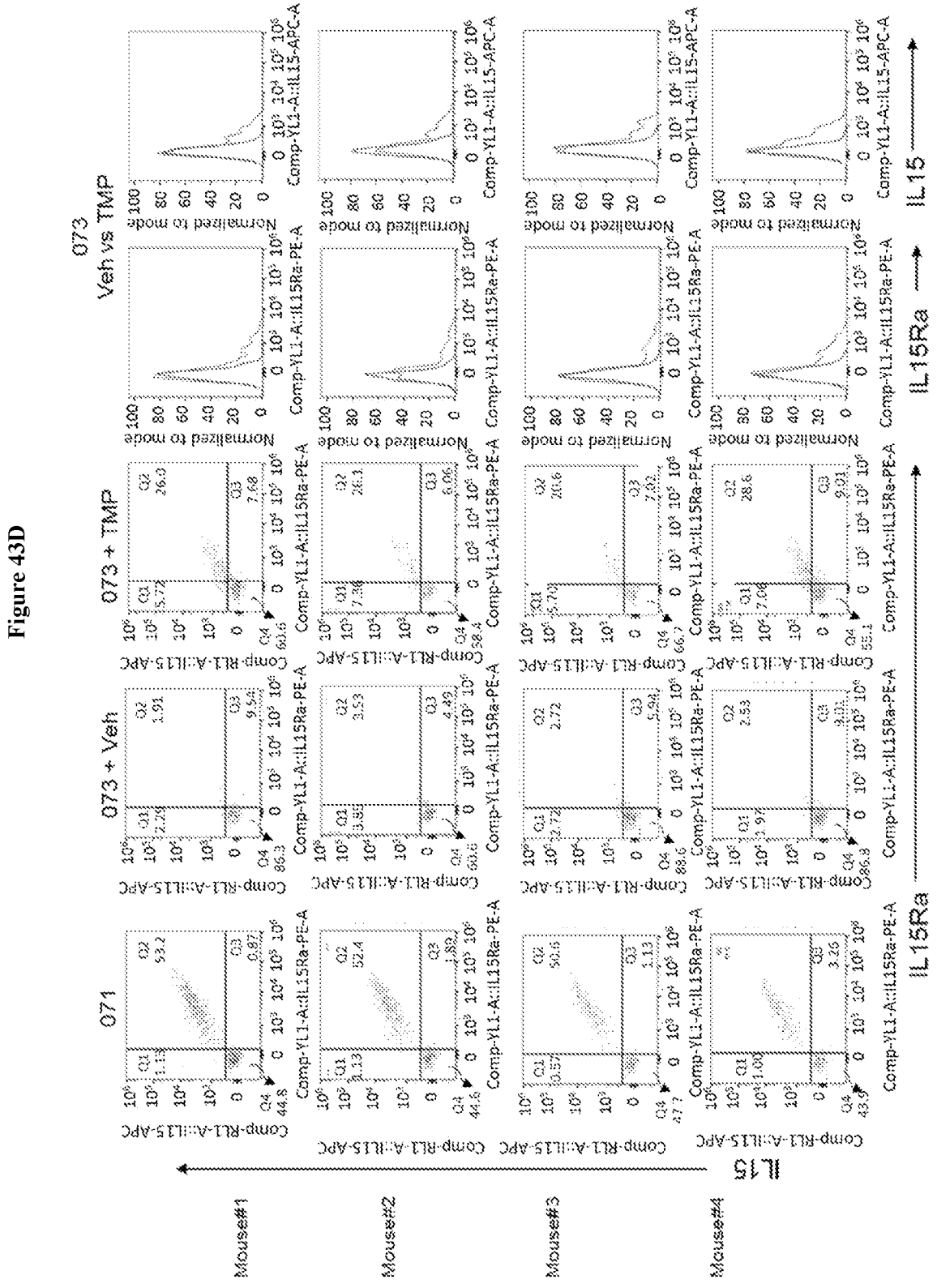

071
073 + Veh
073 + TMP
073
Veh vs TMP
Mouse#1
Mouse#2
Mouse#3
Mouse#4
IL15
IL15Ra
Comp-RL1-A::IL15-APC
Comp-YL1-A::IL15Ra-PE-A
Comp-YL1-A::IL15-APC-A
Normalized to mode

Figure 43E

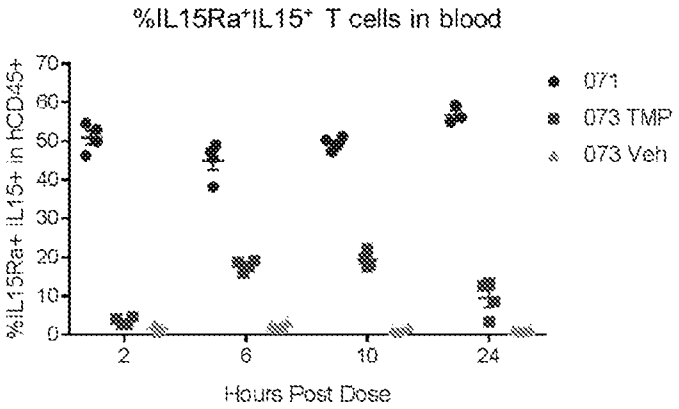


Figure 43F

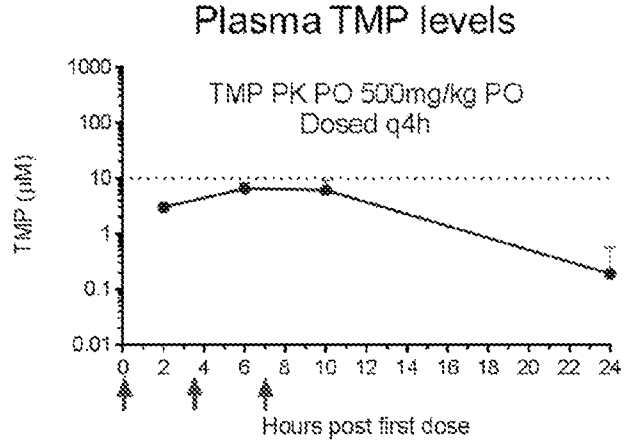
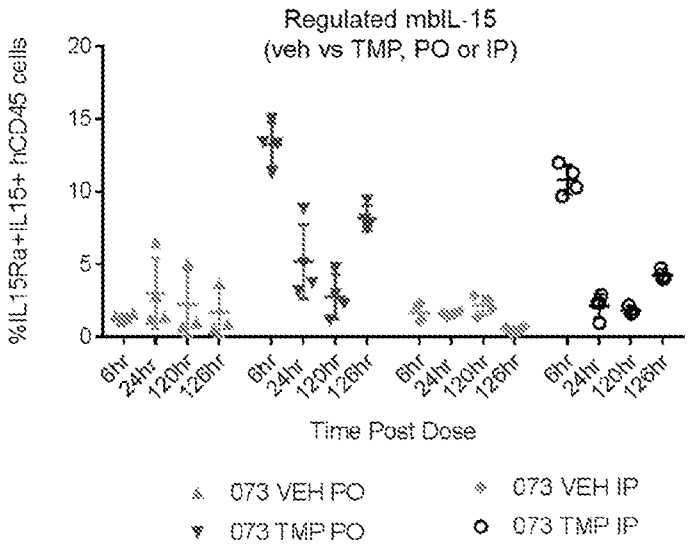


Figure 44



<110> OBSIDIAN THERAPEUTICS, INC.

<120> CD19 COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

<130> 2095.1201PCT

<140> PCT/US2018/XXXXXX
<141> 2018-03-02

<150> 62/484,052
<151> 2017-04-11

<150> 62/466,601
<151> 2017-03-03

<160> 1235

<170> PatentIn version 3.5

<210> 1
<211> 159
<212> PRT
<213> Escherichia coli

<400> 1
Met Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Arg Val Ile Gly Met
1 5 10 15

Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys
20 25 30

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

Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser
50 55 60

Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu
65 70 75 80

Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly
85 90 95

Gly Arg Val Tyr Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu

100 105 110

Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr
115 120 125

Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp
130 135 140

Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
145 150 155

<210> 2
<211> 187
<212> PRT
<213> Homo sapiens

<400> 2
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

```
Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140


Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160


Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175


Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185


<210> 3
<211> 107
<212> PRT
<213> Homo sapiens

<400> 3
Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
1               5                   10                  15


Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp
            20                  25                  30


Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
        35                  40                  45


Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
    50                  55                  60


Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr
65                  70                  75                  80


Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
                85                  90                  95


Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu
            100                 105


<210> 4
```

<211> 327
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Glu Glu Thr Arg Glu Leu Gln Ser Leu Ala Ala Ala Val Val Pro
1               5                  10                  15

Ser Ala Gln Thr Leu Lys Ile Thr Asp Phe Ser Phe Ser Asp Phe Glu
            20                  25                  30

Leu Ser Asp Leu Glu Thr Ala Leu Cys Thr Ile Arg Met Phe Thr Asp
        35                  40                  45

Leu Asn Leu Val Gln Asn Phe Gln Met Lys His Glu Val Leu Cys Arg
    50                  55                  60

Trp Ile Leu Ser Val Lys Lys Asn Tyr Arg Lys Asn Val Ala Tyr His
65                  70                  75                  80

Asn Trp Arg His Ala Phe Asn Thr Ala Gln Cys Met Phe Ala Ala Leu
                85                  90                  95

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

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

Asn Ser Tyr Ile Gln Arg Ser Glu His Pro Leu Ala Gln Leu Tyr Cys
    130                 135                 140

His Ser Ile Met Glu His His His Phe Asp Gln Cys Leu Met Ile Leu
145                 150                 155                 160

Asn Ser Pro Gly Asn Gln Ile Leu Ser Gly Leu Ser Ile Glu Glu Tyr
                165                 170                 175

Lys Thr Thr Leu Lys Ile Ile Lys Gln Ala Ile Leu Ala Thr Asp Leu
            180                 185                 190
```

```
Ala Leu Tyr Ile Lys Arg Arg Gly Glu Phe Phe Glu Leu Ile Arg Lys
        195                 200                 205

Asn Gln Phe Asn Leu Glu Asp Pro His Gln Lys Glu Leu Phe Leu Ala
    210                 215                 220

Met Leu Met Thr Ala Cys Asp Leu Ser Ala Ile Thr Lys Pro Trp Pro
225                 230                 235                 240

Ile Gln Gln Arg Ile Ala Glu Leu Val Ala Thr Glu Phe Phe Asp Gln
                245                 250                 255

Gly Asp Arg Glu Arg Lys Glu Leu Asn Ile Glu Pro Thr Asp Leu Met
            260                 265                 270

Asn Arg Glu Lys Lys Asn Lys Ile Pro Ser Met Gln Val Gly Phe Ile
        275                 280                 285

Asp Ala Ile Cys Leu Gln Leu Tyr Glu Ala Leu Thr His Val Ser Glu
    290                 295                 300

Asp Cys Phe Pro Leu Leu Asp Gly Cys Arg Lys Asn Arg Gln Lys Trp
305                 310                 315                 320

Gln Ala Leu Ala Glu Gln Gln
                325
```

<210> 5
<211> 189
<212> PRT
<213> Homo sapiens

```
<400> 5
Ser Val Glu Ala Val Gln Glu Ile Thr Glu Tyr Ala Lys Ser Ile Pro
1               5                   10                  15

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

Gly Val His Glu Ile Ile Tyr Thr Met Leu Ala Ser Leu Met Asn Lys
```

35 40 45

Asp Gly Val Leu Ile Ser Glu Gly Gln Gly Phe Met Thr Arg Glu Phe
50 55 60

Leu Lys Ser Leu Arg Lys Pro Phe Gly Asp Phe Met Glu Pro Lys Phe
65 70 75 80

Glu Phe Ala Val Lys Phe Asn Ala Leu Glu Leu Asp Asp Ser Asp Leu
85 90 95

Ala Ile Phe Ile Ala Val Ile Ile Leu Ser Gly Asp Arg Pro Gly Leu
100 105 110

Leu Asn Val Lys Pro Ile Glu Asp Ile Gln Asp Asn Leu Leu Gln Ala
115 120 125

Leu Glu Leu Gln Leu Lys Leu Asn His Pro Glu Ser Ser Gln Leu Phe
130 135 140

Ala Lys Leu Leu Gln Lys Met Thr Asp Leu Arg Gln Ile Val Thr Glu
145 150 155 160

His Val Gln Leu Leu Gln Val Ile Lys Lys Thr Glu Thr Asp Met Ser
165 170 175

Leu His Pro Leu Leu Gln Glu Ile Tyr Lys Asp Leu Tyr
180 185

<210> 6
<211> 260
<212> PRT
<213> Homo sapiens

<400> 6
Met Ser His His Trp Gly Tyr Gly Lys His Asn Gly Pro Glu His Trp
1 5 10 15

His Lys Asp Phe Pro Ile Ala Lys Gly Glu Arg Gln Ser Pro Val Asp
20 25 30

```
Ile Asp Thr His Thr Ala Lys Tyr Asp Pro Ser Leu Lys Pro Leu Ser
        35                  40                  45

Val Ser Tyr Asp Gln Ala Thr Ser Leu Arg Ile Leu Asn Asn Gly His
    50                  55                  60

Ala Phe Asn Val Glu Phe Asp Asp Ser Gln Asp Lys Ala Val Leu Lys
65                  70                  75                  80

Gly Gly Pro Leu Asp Gly Thr Tyr Arg Leu Ile Gln Phe His Phe His
                85                  90                  95

Trp Gly Ser Leu Asp Gly Gln Gly Ser Glu His Thr Val Asp Lys Lys
            100                 105                 110

Lys Tyr Ala Ala Glu Leu His Leu Val His Trp Asn Thr Lys Tyr Gly
        115                 120                 125

Asp Phe Gly Lys Ala Val Gln Gln Pro Asp Gly Leu Ala Val Leu Gly
    130                 135                 140

Ile Phe Leu Lys Val Gly Ser Ala Lys Pro Gly Leu Gln Lys Val Val
145                 150                 155                 160

Asp Val Leu Asp Ser Ile Lys Thr Lys Gly Lys Ser Ala Asp Phe Thr
                165                 170                 175

Asn Phe Asp Pro Arg Gly Leu Leu Pro Glu Ser Leu Asp Tyr Trp Thr
            180                 185                 190

Tyr Pro Gly Ser Leu Thr Thr Pro Pro Leu Leu Glu Cys Val Thr Trp
        195                 200                 205

Ile Val Leu Lys Glu Pro Ile Ser Val Ser Ser Glu Gln Val Leu Lys
    210                 215                 220

Phe Arg Lys Leu Asn Phe Asn Gly Glu Gly Glu Pro Glu Glu Leu Met
225                 230                 235                 240
```

```
Val Asp Asn Trp Arg Pro Ala Gln Pro Leu Lys Asn Arg Gln Ile Lys
                245                 250                 255


Ala Ser Phe Lys
            260


<210> 7
<211> 231
<212> PRT
<213> Homo sapiens

<400> 7
Met Ala Gly Lys Lys Val Leu Ile Val Tyr Ala His Gln Glu Pro Lys
1               5                   10                  15


Ser Phe Asn Gly Ser Leu Lys Asn Val Ala Val Asp Glu Leu Ser Arg
            20                  25                  30


Gln Gly Cys Thr Val Thr Val Ser Asp Leu Tyr Ala Met Asn Leu Glu
        35                  40                  45


Pro Arg Ala Thr Asp Lys Asp Ile Thr Gly Thr Leu Ser Asn Pro Glu
    50                  55                  60


Val Phe Asn Tyr Gly Val Glu Thr His Glu Ala Tyr Lys Gln Arg Ser
65                  70                  75                  80


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


Leu Val Ile Phe Gln Phe Pro Leu Tyr Trp Phe Ser Val Pro Ala Ile
            100                 105                 110


Leu Lys Gly Trp Met Asp Arg Val Leu Cys Gln Gly Phe Ala Phe Asp
        115                 120                 125


Ile Pro Gly Phe Tyr Asp Ser Gly Leu Leu Gln Gly Lys Leu Ala Leu
    130                 135                 140


Leu Ser Val Thr Thr Gly Gly Thr Ala Glu Met Tyr Thr Lys Thr Gly
```

145 150 155 160

Val Asn Gly Asp Ser Arg Tyr Phe Leu Trp Pro Leu Gln His Gly Thr
165 170 175

Leu His Phe Cys Gly Phe Lys Val Leu Ala Pro Gln Ile Ser Phe Ala
180 185 190

Pro Glu Ile Ala Ser Glu Glu Glu Arg Lys Gly Met Val Ala Ala Trp
195 200 205

Ser Gln Arg Leu Gln Thr Ile Trp Lys Glu Glu Pro Ile Pro Cys Thr
210 215 220

Ala His Trp His Phe Gly Gln
225 230

<210> 8
<211> 159
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 8
Met Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met
1 5 10 15

Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys
20 25 30

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

Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser
50 55 60

Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu
65 70 75 80

Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly
85 90 95

Gly Arg Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu
100 105 110

Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr
115 120 125

Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp
130 135 140

Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
145 150 155

<210> 9
<211> 158
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 9
Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu
1 5 10 15

Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg
20 25 30

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

Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln
50 55 60

Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala
65 70 75 80

Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly

85 90 95

Arg Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr
100 105 110

His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu
115 120 125

Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala
130 135 140

Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
145 150 155

<210> 10
<211> 158
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 10
Ile Ser Leu Ile Ala Ala Leu Ala Val Asp His Val Ile Gly Met Glu
1 5 10 15

Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg
20 25 30

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

Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln
50 55 60

Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala
65 70 75 80

Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly
85 90 95

Arg Val Tyr Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr
100 105 110

His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Lys
115 120 125

Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala
130 135 140

Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
145 150 155

<210> 11
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 11
Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
1 5 10 15

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp
20 25 30

Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
35 40 45

Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
50 55 60

Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr
65 70 75 80

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
85 90 95

Leu Val Phe Asp Val Glu Leu Leu Lys Pro Glu

100 105

<210> 12
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 12
Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
1 5 10 15

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly Asp
20 25 30

Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
35 40 45

Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
50 55 60

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

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
85 90 95

Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
100 105

<210> 13
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 13
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly

1 5 10 15

Val Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 14
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 14

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Ser Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 15
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 15
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asp Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile

165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 16
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 16
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Arg Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 17
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 17
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Val Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His

115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 18
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 18
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 19
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 19
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu

65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Tyr His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 20
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 20
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

```
Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Ile Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 21
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 21

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                   10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
```

20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Glu Asn Asp
180 185

<210> 22
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 22

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asp Asp
            180                 185
```

<210> 23
<211> 187
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 23

```
Met Val Gly Ser Leu Asn Arg Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Cys Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
```

180 185

<210> 24
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 24
Met Val Gly Ser Leu Asn Cys Ile Val Val Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala Tyr Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 25
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 25
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Lys Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu

130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 26
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 26
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Thr Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Ile Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 27
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 27
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Ala Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ala Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp

85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 28
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 28
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Gly Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Phe
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 29
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 29
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Thr Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln

35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 30
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 30
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

```
Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Asn Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 31
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

destabilizing domain (DD)

<400> 31

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

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

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 32

<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 32

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Ala Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Ala Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175
```

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 33
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 33
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Ala Ile Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu

145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 34
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 34
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Phe Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 35
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 35
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met

100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly Arg Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Gly
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 36
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 36
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Arg Arg Ile Met Gln Asp Leu Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 37
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 37
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys

50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys His Lys Phe Gly Val Tyr Glu Lys Asn Asp
180 185

<210> 38
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 38
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

```
Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val His Glu Glu Asn Asp
            180                 185
```

<210> 39
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 39

```
Met Val Gly Ser Leu Asn Cys Ile Ala Ala Val Ser Gln Asn Met Gly
```

1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Arg Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Leu Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 40
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 40

```
Met Val Gly Ser Leu Asn Cys Val Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Glu Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Cys Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 41
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 41
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Ser Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Ala Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Cys Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile

165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 42
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 42
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Glu Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Leu Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

```
Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160


Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175


Lys Tyr Lys Phe Gly Val Tyr Glu Lys Asn Asp
            180                 185


<210> 43
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      destabilizing domain (DD)

<400> 43
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                   10                  15


Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30


Arg Tyr Phe Phe Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45


Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60


Phe Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80


Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95


Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110


Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His
```

115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 44
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 44
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Arg Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Val Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Cys Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 45
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 45
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu

65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Ala Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Met Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Arg Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 46
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 46
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Phe Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

```
Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50                  55                  60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Phe Met Asn His Pro
        115                 120                 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
    130                 135                 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185


<210> 47
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      destabilizing domain (DD)

<400> 47
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                   10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
```

20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asp Leu Val Ile Met Gly Lys Lys Thr Trp Ser Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Gly Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 48
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 48

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Glu Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Val Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Thr
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 49
<211> 449
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 49

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


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


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


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60


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


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


Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


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


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


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
```

```
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
```

385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 50
<211> 223
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 50
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

```
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


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


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


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220


<210> 51
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 51
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15


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


Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu
```

```
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Asn Tyr His Leu Glu Asn Glu Val Ala
    130                 135                 140

Arg Leu Lys Lys Leu Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
145                 150                 155                 160

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
                165                 170                 175

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
            180                 185                 190

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
        195                 200                 205

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
    210                 215                 220

Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225                 230
```

<210> 52

<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 52
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Asn Tyr His Leu Glu Asn Glu Val Ala
130 135 140

Arg Leu Lys Lys Leu Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
145 150 155 160

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
165 170 175

```
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
            180                 185                 190


Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
        195                 200                 205


Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
    210                 215                 220


Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
225                 230                 235                 240


Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
                245                 250                 255


Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260                 265                 270


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
        275                 280                 285


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290                 295                 300


Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
305                 310                 315                 320


Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                325                 330                 335


Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
            340                 345                 350


Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        355                 360                 365


Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    370                 375                 380
```

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385 390 395 400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
405 410 415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
420 425 430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
435 440 445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 53
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 53
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys

85 90 95

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

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

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Gly
210 215 220

Gly Gly Ser Asn Tyr His Leu Glu Asn Glu Val Ala Arg Leu Lys Lys
225 230 235 240

Leu

<210> 54
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 54

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

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

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

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
```

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Gly Gly Gly Ser Asn Tyr His Leu Glu Asn Glu Val Ala Arg Leu Lys
225                 230                 235                 240

Lys Leu Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305                 310                 315                 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415
```

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 55
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 55
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln

100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 56
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic heavy chain variable domain

<400> 56
Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50 55 60

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

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 57
<211> 464
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

heavy chain variable domain

<400> 57

```
Met Glu Trp Ser Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1               5                  10                  15

Val His Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr
    130                 135                 140

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
```

195 200 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
210 215 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225 230 235 240

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
245 250 255

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
260 265 270

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
275 280 285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
290 295 300

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305 310 315 320

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
325 330 335

Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
340 345 350

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
355 360 365

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
370 375 380

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385 390 395 400

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp

405 410 415

Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser
420 425 430

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
435 440 445

Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> 58
<211> 137
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 58
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

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

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

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

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

Arg Ser Asp Pro Leu Ile Asn Lys Glu Arg Gly Gly Gly Gly Ser Gly
        115   120   125

Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130   135

<210> 59
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 59
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
            20   25   30

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

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50   55   60

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

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

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
            100   105   110

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

<210> 60

<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 60
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

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

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

Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
100 105 110

Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
115 120 125

Ser Ser
130

<210> 61
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

heavy chain variable domain

<400> 61
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
115 120 125

<210> 62
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 62
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125


<210> 63
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 63
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15


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


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


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60


Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
```

65 70 75 80

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

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

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

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr
225

<210> 64
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<220>
<221> MOD_RES
<222> (64)..(65)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (68)..(69)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (93)..(93)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Any amino acid

<400> 64
Gln 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 Gly 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 Xaa
    50   55   60

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

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

Ala Xaa

<210> 65
<211> 125

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<220>
<221> MOD_RES
<222> (76)..(76)
<223> Any amino acid

<400> 65
Gln 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 Gly 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 Xaa Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
115 120 125

<210> 66
<211> 125
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 66

```
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 67
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 67

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125


<210> 68
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 68
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 69
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 69
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115   120   125

<210> 70
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 70
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 Gly Phe Thr Phe Asp Asp Tyr
            20   25   30

Ala Met His Trp Val Arg Leu 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 Lys Asn Ser Leu Phe
65   70   75   80

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

Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 71
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 71
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
115 120 125

<210> 72
<211> 464
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 72
Met Glu Trp Ser Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15

```
Val His Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr
    130                 135                 140

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
145                 150                 155                 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
        195                 200                 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
    210                 215                 220
```

```
Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225                 230                 235                 240


Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
                245                 250                 255


Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
            260                 265                 270


Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
        275                 280                 285


Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
    290                 295                 300


Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305                 310                 315                 320


Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
                325                 330                 335


Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350


Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
        355                 360                 365


Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
    370                 375                 380


Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
385                 390                 395                 400


Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
                405                 410                 415


Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser
            420                 425                 430
```

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
435 440 445

Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> 73
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic heavy chain variable domain

<400> 73
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 74
<211> 218

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 74

```
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 Val Ser Leu Pro Asp Tyr
            20                  25                  30


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


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


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


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


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


Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125


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


Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160


Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
```

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215

<210> 75
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic heavy chain variable domain

<400> 75
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 Val Ser Leu Pro Asp Tyr
20 25 30

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

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

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

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

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

```
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140


Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160


Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175


Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190


Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205


Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215


<210> 76
<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 76
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15


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


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


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60
```

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Asn Tyr His Leu Glu Asn Glu Val Ala
    130                 135                 140

Arg Leu Lys Lys Leu Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
145                 150                 155                 160

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
                165                 170                 175

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
            180                 185                 190

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
        195                 200                 205

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
    210                 215                 220

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
225                 230                 235                 240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
                245                 250                 255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260                 265                 270
```

```
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
        275                 280                 285

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290                 295                 300

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
305                 310                 315                 320

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                325                 330                 335

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
            340                 345                 350

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        355                 360                 365

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    370                 375                 380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385                 390                 395                 400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
                405                 410                 415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
            420                 425                 430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
        435                 440                 445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460
```

<210> 77
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
heavy chain variable domain

<400> 77
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

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

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

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

Gly Gly Gly Ser Asn Tyr His Leu Glu Asn Glu Val Ala Arg Leu Lys
225 230 235 240

Lys Leu

<210> 78
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic heavy chain variable domain

<400> 78
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

```
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

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

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Gly Gly Gly Ser Asn Tyr His Leu Glu Asn Glu Val Ala Arg Leu Lys
225                 230                 235                 240

Lys Leu Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305                 310                 315                 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            420                 425                 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        435                 440                 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                 455                 460

Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 79
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic heavy chain variable domain

<400> 79
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1   5   10   15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50   55   60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Ser Val Thr Val
        115

<210> 80
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      heavy chain variable domain

<400> 80
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val
115

<210> 81
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 81
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50 55 60

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

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

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

<210> 82
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 82
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

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

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

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

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

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

```
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335
```

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 83
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 83
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

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

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

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

```
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Val Thr Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95


Leu Ser Asp Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> 84
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 84
Glu Ile Val Met Thr Gln Ser Pro Ser Ser Leu Pro Ala Ser Val Gly
1               5                   10                  15


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


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


Tyr Ala Ala Ser Asn Leu Gln Ile 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 Phe Cys Gln Gln Ser Tyr Ile Thr Pro Pro
                85                  90                  95


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

<210> 85
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 85

```
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 Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175
```

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 86
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 86
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 Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Gly Gly Gly Gly Ser Asn Tyr His
165 170 175

Leu Glu Asn Glu Val Ala Arg Leu Lys Lys Leu Gly Gly Gly Gly Ser
180 185 190

Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
195 200 205

Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
210 215 220

Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 87
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 87
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
            100                 105


<210> 88
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 88
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
100 105

<210> 89
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic light chain variable domain

<400> 89
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

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

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

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

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

Arg Ala Asp
115

<210> 90
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 90
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
100 105

<210> 91
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 91
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

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


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


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


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


<210> 92
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 92
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
1               5                   10                  15


Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
            20                  25                  30


Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
        35                  40                  45


Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser
    50                  55                  60


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


Ala Asp Tyr Phe Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu
                85                  90                  95
```

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 93
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic light chain variable domain

<400> 93
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
20 25 30

Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
35 40 45

Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser
50 55 60

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

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

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 94
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic light chain variable domain

<400> 94

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

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

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

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

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser
85 90 95

Leu Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 95
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 95
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15

Glu Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

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

Ile Tyr Asp Asn Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

```
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65                  70                  75                  80


Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu
                85                  90                  95


Ser Ala Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100                 105


<210> 96
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 96
Ser Tyr Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1               5                   10                  15


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


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


Asp Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60


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


Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn
                85                  90                  95


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 97
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 97
Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 98
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 98
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Thr Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr
            20   25   30

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

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

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

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

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

<210> 99
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 99
Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

Gly 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 Gln Gln Ser Tyr Ser Thr Pro Gln
85 90 95

Ala Tyr Thr Phe Gly Gln Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 100
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 100
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

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

Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65 70 75 80

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

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

<210> 101
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)..(9)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (93)..(93)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (104)..(104)
<223> Any amino acid

<400> 101
Gln Ser Val Leu Xaa Xaa Pro Xaa Xaa Ala Ser Gly Ser Pro Gly Gln
1 5 10 15

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

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

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

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

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

Lys Tyr Val Phe Gly Thr Gly Xaa Lys Val Thr Val Leu

100 105

<210> 102
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<220>
<221> MOD_RES
<222> (61)..(61)
<223> Any amino acid

<400> 102
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
35 40 45

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

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

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

Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 103
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 103
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
35 40 45

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

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

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

Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 104
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 104
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe
20 25 30

Asp Tyr Val Ser Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu

35 40 45

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

Ser Gly Ala Lys Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

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

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

<210> 105
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 105
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
35 40 45

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

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

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

Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
100 105 110

<210> 106
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 106
Gln Ser Val Leu Thr Gln Pro Arg Ser Leu Ser Gly Ser Pro Gly Gln
1 5 10 15

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

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

Met Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Tyr Thr Phe Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 107
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 107
Gln Leu Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Phe Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr
20 25 30

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

Leu Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

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

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

Tyr Thr Tyr Trp Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 108
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 108
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
20 25 30

Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
35 40 45

Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser

50 55 60

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

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

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 109
<211> 99
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 109
Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

Thr Val Asn Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

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

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Val Val

<210> 110
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 110
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

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

Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65 70 75 80

Thr Gly Asp Glu Gly Asp Tyr Tyr Cys Gly Thr Trp Asp Ile Ser Leu
85 90 95

Arg Phe Gly Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 111
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 111
Gln Ser Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

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

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

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

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

Thr His Thr Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            100   105   110

<210> 112
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 112
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1   5   10   15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
            20   25   30

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

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50   55   60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr

65 70 75 80

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

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
100 105 110

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

<210> 113
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 113
Met Arg Cys Leu Ala Glu Phe Leu Gly Leu Leu Val Leu Trp Ile Pro
1 5 10 15

Gly Ala Ile Gly Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro
20 25 30

Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser
35 40 45

Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg
50 55 60

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe
85 90 95

Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
100 105 110

```
Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys
        115                 120                 125


Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro
    130                 135                 140


Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe
145                 150                 155                 160


Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp
                165                 170                 175


Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp
            180                 185                 190


Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys
        195                 200                 205


Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys
    210                 215                 220


Thr Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230                 235


<210> 114
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 114
Gln Ala Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Val Thr Ile Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His
            20                  25                  30


Arg Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu
```

35 40 45

Met Ile Tyr Asp Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile
85 90 95

Ser Pro Asn Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 115
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 115
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe
20 25 30

Asp Tyr Val Ser Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu
35 40 45

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

Ser Gly Ala Lys Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

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

Pro Thr Phe Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 116
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 116
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

Asn Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu
65 70 75 80

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

Leu Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 117
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 117
Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Gly 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 Gln Gln Ser Tyr Ser Thr Pro Gln
85 90 95

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

<210> 118
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 118
Ala Ile Arg Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Phe Asp Ala Ser Arg 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

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

Phe Thr Phe Gly Pro Gly Thr Arg Val Asp Leu Lys
100 105

<210> 119
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 119
Asp Ile Gln Leu Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Asp Ala Ser Asn Leu Glu Thr 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 Tyr Asp Asn Leu Pro Leu
85 90 95

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

<210> 120
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 120
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Thr Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr
20 25 30

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

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

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

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

Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 121
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
light chain variable domain

<400> 121
Gln Ala Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His
            20   25   30

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

Met Ile Tyr Asp Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50   55   60

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile
                85   90   95

Ser Pro Asn Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            100   105   110

<210> 122
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      light chain variable domain

<400> 122
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr

65 70 75 80

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

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 123
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 123
Trp Ser His Pro Gln Phe Glu Lys Gly Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Gly Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser
20 25 30

Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser
35 40 45

Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu
50 55 60

Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe
65 70 75 80

Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu
85 90 95

Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu
100 105 110

```
Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr
        115                 120                 125


Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu
    130                 135                 140


Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160


Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175


Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205


Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220


Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240


His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Ser Val Thr Val Ser Ser
            260


<210> 124
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 124
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 Gly Ser Gly Ser
            100                 105                 110

Gly Asn Trp Ser His Pro Gln Phe Glu Lys Gly Ser Gly Ser Gly Glu
        115                 120                 125

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

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160

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

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

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

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
```

210 215 220

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

Thr Ser Val Thr Val Ser Ser
245

<210> 125
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 125
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
115 120 125

```
Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140


Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160


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


Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190


Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205


Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220


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


Ser Ser
```

<210> 126
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 126

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


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


Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
```

```
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160

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

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

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

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

Gly Thr Lys Leu Glu Ile Lys
```

245

<210> 127
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 127
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu
130 135 140

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

```
Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln
                165                 170                 175


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


Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn
        195                 200                 205


Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220


Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn Trp Val Phe Gly
225                 230                 235                 240


Gly Gly Thr Lys Leu Thr Val Leu
                245


<210> 128
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 128
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


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


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


Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
```

65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
115 120 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
130 135 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145 150 155 160

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

Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
180 185 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
195 200 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

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

Ser Ser

<210> 129
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 129

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

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
195 200 205

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

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

Ile Lys

<210> 130
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 130
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
115 120 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
130 135 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145 150 155 160

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

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
180 185 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
195 200 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

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

Ser Ser

<210> 131
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 131
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205

Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Phe
    210                 215                 220
```

Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 132
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 132
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

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

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

Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
100 105 110

Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
115 120 125

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

130 135 140

Ser Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145 150 155 160

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

Tyr Leu Asn Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Glu Leu Leu
180 185 190

Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
195 200 205

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Val Gln
210 215 220

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

Leu Thr Phe Gly Pro Gly Thr Lys Val Thr Ile Arg
245 250

<210> 133
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 133
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160

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

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

Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240

Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 134
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 134
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
130 135 140

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

Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr

165 170 175

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

Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
195 200 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225 230 235 240

Gly Gln Gly Thr Lys Leu Asp Ile Lys
245

<210> 135
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 135
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160


Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175


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


Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205


Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220


Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Asn Arg Asp Trp
225                 230                 235                 240


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 136
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
```

single chain variable fragment

<400> 136

```
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
```

195 200 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 137
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 137
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

```
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


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


Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 138
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 138
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
```

225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 139
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 139
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

```
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 140
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 140
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
165 170 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
180 185 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 141

<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<220>
<221> MOD_RES
<222> (76)..(76)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (201)..(201)
<223> Any amino acid

<400> 141

```
Gln 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 Gly 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 Xaa Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
```

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

Ser Cys Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
165 170 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
180 185 190

Val Thr Val Arg Pro Ser Gly Val Xaa Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 142
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 142
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 143
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 143
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145 150 155 160

Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
165 170 175

Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
180 185 190

Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
195 200 205

Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
210 215 220

Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225 230 235 240

Phe Gly Thr Gly Thr Lys Leu Asp Ile Lys
245 250

<210> 144
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 144
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
                245                 250
```

<210> 145
<211> 236
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 145
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gln Ser Val
115 120 125

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

Ile Ala Cys Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr Asn Tyr Val
145 150 155 160

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
165 170 175

Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
180 185 190

Lys Ser Gly Asn Thr Ala Phe Leu Thr Ile Ser Gly Leu Gln Ala Glu
195 200 205

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

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235

<210> 146
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 146
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Leu Val Leu
    130                 135                 140


Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Phe
145                 150                 155                 160


Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr Asp His Val Ser
                165                 170                 175


Trp Tyr Gln His His Pro Gly Lys Gly Pro Lys Leu Leu Ile Tyr Asp
            180                 185                 190


Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Cys Ser Phe Ala Gly Tyr Tyr Thr Tyr Trp
225                 230                 235                 240


Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250


<210> 147
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 147
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205

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

Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro Phe Gly Gly Gly
225                 230                 235                 240
```

Thr Lys Leu Thr Val Leu
245

<210> 148
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 148
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
130 135 140

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

```
Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp
                165                 170                 175


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


Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205


Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu
    210                 215                 220


Ala Glu Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Asn Val Val
225                 230                 235


<210> 149
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 149
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160


Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175


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


Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205


Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220


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


Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250


<210> 150
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment
```

<400> 150
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 Gly Phe Thr Phe Asp Asp Tyr
            20   25   30

Ala Met His Trp Val Arg Leu 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 Lys Asn Ser Leu Phe
65   70   75   80

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

Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115   120   125

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

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

Ser Cys Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr Thr Ser Val Ser
                165   170   175

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

Val Thr Gln Arg Pro Ser Gly Val Pro Asn Arg Phe Ser Gly Ser Lys
        195   200   205

```
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Asp Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Glu Ala Pro Thr His Thr Tyr
225                 230                 235                 240


Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 151
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 151
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


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


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


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
    50                  55                  60


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


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


Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110
```

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

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
130 135 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145 150 155 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
195 200 205

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

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

Ile Lys

<210> 152
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 152
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
        195                 200                 205

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

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240
```

Ile Lys

<210> 153
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 153
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145 150 155 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
165 170 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
180 185 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
195 200 205

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

Cys Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 154
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 154
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

```
Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160

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

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

Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240

Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245
```

<210> 155
<211> 249

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 155

```
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140


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


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

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


Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205


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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240


Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245


<210> 156
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 156
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 157
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 157

```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                  10                  15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205
```

```
Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

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

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415
```

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 158
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 158
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
        115                 120                 125


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


Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160


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


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
            180                 185                 190


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


Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220


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


Thr Leu Val Thr Val Ser Ser
                245
```

<210> 159
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 159

```
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

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

Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190

Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
```

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

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225 230 235 240

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 160
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 160
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205


Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240


Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 161
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 161
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu
    130                 135                 140

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

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

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

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

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

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

Gly Thr Lys Val Glu Ile Lys
245

<210> 162
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 162
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
130 135 140

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

```
Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser His Tyr Leu Ala Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Phe Asp Ala Ser
            180                 185                 190


Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Met Phe Thr Phe Gly
225                 230                 235                 240


Pro Gly Thr Arg Val Asp Leu Lys
                245


<210> 163
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 163
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 Gly Gly Gly Ser
            100                 105                 110


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


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


Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160


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


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


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


Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220


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


Ser Ser
```

<210> 164
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 164
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Phe Val Ser
165 170 175

Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe Leu Ile Tyr Asp
180 185 190

Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys
195 200 205

Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp
210 215 220

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 165
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 165
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
        115                 120                 125


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


Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160


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


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
            180                 185                 190


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


Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220


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


Thr Leu Val Thr Val Ser Ser
                245


<210> 166
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 166
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Phe Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

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

Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp
    210                 215                 220
```

Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Ser Val Val
225 230 235 240

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 167
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 167
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
100 105 110

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

```
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ala Ala
    130                 135                 140


Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg
145                 150                 155                 160


Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp
                165                 170                 175


Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met
            180                 185                 190


Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


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


Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly
225                 230                 235                 240


Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
                245                 250


<210> 168
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 168
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


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


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

```
Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160

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

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

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

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

Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 169
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 169
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
130 135 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145 150 155 160

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

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

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

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

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

Gly Thr Lys Leu Glu Ile Lys
245

<210> 170
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 170
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Glu Val Thr Ile
145                 150                 155                 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175

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

Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220

Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu Ser Ala Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Val Thr Val Leu
                245
```

<210> 171
<211> 251
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 171

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


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


Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190
```

Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225 230 235 240

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 172
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 172
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
        115                 120                 125


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


Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160


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


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
            180                 185                 190


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


Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220


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


Thr Leu Val Thr Val Ser Ser
                245


<210> 173
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 173
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15
```

```
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser
            20                  25                  30

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

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

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

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

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

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

Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
    130                 135                 140

Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser
145                 150                 155                 160

Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys Ser Gly Thr Ser
                165                 170                 175

Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro
            180                 185                 190

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Phe Leu Thr Ile
        195                 200                 205

Asn Asn Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
    210                 215                 220
```

Asn Ile Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
225 230 235 240

Arg

<210> 174
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 174
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu
130 135 140

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


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


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


Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn
        195                 200                 205


Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220


Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn Trp Val Phe Gly
225                 230                 235                 240


Gly Gly Thr Lys Leu Thr Val Leu
                245


<210> 175
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 175
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205

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

Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225                 230                 235                 240

Thr Lys Leu Thr Val Leu
                245
```

<210> 176
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 176

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


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


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


Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
    50                  55                  60


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


Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
            100                 105                 110


Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
        115                 120                 125


Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140


Ser Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145                 150                 155                 160


Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser
                165                 170                 175
```

```
Tyr Leu Asn Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Glu Leu Leu
            180                 185                 190


Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Val Gln
    210                 215                 220


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


Leu Thr Phe Gly Pro Gly Thr Lys Val Thr Ile Arg
                245                 250


<210> 177
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 177
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160

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

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

Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240

Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 178
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 178
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50   55   60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115   120   125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130   135   140

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

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

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

Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195   200   205

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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240


Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245


<210> 179
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 179
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
```

```
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160


Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175


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


Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205


Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220


Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Asn Arg Asp Trp
225                 230                 235                 240


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 180
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 180
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
```

```
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 181
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 181
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
```

```
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 182
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment


<220>
<221> MOD_RES
<222> (64)..(65)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (68)..(69)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (93)..(93)
<223> Any amino acid
```

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (102)..(102)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (104)..(104)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (113)..(113)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (145)..(146)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (148)..(149)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (233)..(233)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (244)..(244)
<223> Any amino acid

<400> 182
Gln 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 Gly 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 Xaa
    50                  55                  60

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

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

Ala Xaa Asp Gln Gly Xaa His Xaa Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Xaa Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Xaa Xaa Pro Xaa Xaa Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Val
145                 150                 155                 160

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

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly
            180                 185                 190

Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Asp Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln Val Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Ser Ser Xaa Ala Gly Arg Lys Tyr Val Phe
225                 230                 235                 240

Gly Thr Gly Xaa Lys Val Thr Val Leu
                245
```

<210> 183
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 183
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

```
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 184
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 184
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 185
<211> 252
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 185
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
165 170 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
180 185 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 186
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<220>
<221> MOD_RES
<222> (76)..(76)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (201)..(201)
<223> Any amino acid

<400> 186
Gln 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 Gly 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 Xaa Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Xaa Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250

<210> 187
<211> 252
<212> PRT
```

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 187

```
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


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


Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
```

180 185 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 188
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 188
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205


Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240


Phe Gly Thr Gly Thr Lys Leu Asp Ile Lys
                245                 250


<210> 189
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 189
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
```

210 215 220

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
245 250

<210> 190
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 190
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gln Ser Val
115 120 125

```
Leu Thr Gln Pro Arg Ser Leu Ser Gly Ser Pro Gly Gln Ser Val Thr
    130                 135                 140


Ile Ala Cys Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr Asn Tyr Val
145                 150                 155                 160


Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
                165                 170                 175


Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
            180                 185                 190


Lys Ser Gly Asn Thr Ala Phe Leu Thr Ile Ser Gly Leu Gln Ala Glu
        195                 200                 205


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


Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225                 230                 235


<210> 191
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 191
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Phe
145                 150                 155                 160

Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr Asp His Val Ser
                165                 170                 175

Trp Tyr Gln His His Pro Gly Lys Gly Pro Lys Leu Leu Ile Tyr Asp
            180                 185                 190

Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Cys Ser Phe Ala Gly Tyr Tyr Thr Tyr Trp
225                 230                 235                 240

Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250
```

<210> 192

<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 192

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175
```

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
180 185 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
195 200 205

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

Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 193
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 193
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
130 135 140

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

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp
165 170 175

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

Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
195 200 205

Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu
210 215 220

Ala Glu Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Asn Val Val
225 230 235

<210> 194
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 194
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175

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

Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220
```

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

Phe Gly Gly Gly Thr Lys Val Thr Val Leu
245 250

<210> 195
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 195
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 Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Leu 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 Lys Asn Ser Leu Phe
65 70 75 80

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

Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu

130 135 140

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

Ser Cys Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr Thr Ser Val Ser
165 170 175

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

Val Thr Gln Arg Pro Ser Gly Val Pro Asn Arg Phe Ser Gly Ser Lys
195 200 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Asp Asp
210 215 220

Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Glu Ala Pro Thr His Thr Tyr
225 230 235 240

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 196
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 196
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 Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255
```

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

Pro

<210> 197
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 197
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 Lys Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys
50 55 60

Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

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

Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala
100 105 110

Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly

130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
145 150 155 160

Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr
165 170 175

Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
180 185 190

Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His Thr Ser
195 200 205

Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala
225 230 235 240

Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Leu Glu Ile Thr Arg Ser Asp Pro Thr Ser Ser
260 265 270

<210> 198
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 198
Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

```
Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
        35                  40                  45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
    50                  55                  60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65                  70                  75                  80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
                85                  90                  95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
            100                 105                 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr
        115                 120                 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
    130                 135                 140

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

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

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
            180                 185                 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
        195                 200                 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
    210                 215                 220

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

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ser Asp Pro
275

<210> 199
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 199
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly

```
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205

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

Cys Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225                 230                 235                 240

Thr Lys Leu Thr Val Leu
                245


<210> 200
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 200
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160

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

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

Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240
```

Gly Gln Gly Thr Lys Leu Asp Ile Lys
245

<210> 201
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 201
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
130 135 140

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

145 150 155 160

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

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

Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
195 200 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225 230 235 240

Gly Gln Gly Thr Lys Leu Glu Ile Lys
245

<210> 202
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 202
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


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


Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 203
<211> 251
<212> PRT
```

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 203
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

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

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

Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
165 170 175

Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp

180 185 190

Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225 230 235 240

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 204
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 204
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205


Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240


Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 205
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 205
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
```

```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu
    130                 135                 140

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

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

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

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

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
```

210 215 220

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

Gly Thr Lys Val Glu Ile Lys
245

<210> 206
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 206
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140


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


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


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Phe Asp Ala Ser
            180                 185                 190


Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Met Phe Thr Phe Gly
225                 230                 235                 240


Pro Gly Thr Arg Val Asp Leu Lys
                245


<210> 207
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 207
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Phe Val Ser
                165                 170                 175

Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe Leu Ile Tyr Asp
            180                 185                 190

Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp
    210                 215                 220

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
```

245 250

<210> 208
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 208
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

```
Phe Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


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


Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Ser Val Val
225                 230                 235                 240


Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 209
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 209
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 Gly 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 Lys Asn Ser Leu Phe
```

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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Glu Val Thr Ile
145 150 155 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
165 170 175

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

Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
195 200 205

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu Ser Ala Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Val Thr Val Leu
245

<210> 210
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 210

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

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

Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190
```

Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
195 200 205

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

Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225 230 235 240

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 211
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 211
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe

100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
130 135 140

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

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

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

Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
195 200 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225 230 235 240

Gly Gln Gly Thr Lys Leu Asp Ile Lys
245

<210> 212
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 212
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

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

Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220
```

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

Ser Ser

<210> 213
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 213
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

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
245

<210> 214
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 214
Gln Val Gln Leu Leu Glu Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20 25 30

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

Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50 55 60

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

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

Ala Arg Lys Thr Ile Ser Ser Val Val Asp Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr
115

<210> 215
<211> 438
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 215
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

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
100 105 110

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
115 120 125

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
145 150 155 160

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
165 170 175

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
180 185 190

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
195 200 205

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
210 215 220

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
225 230 235 240

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
245 250 255

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
260 265 270

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
275 280 285

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln

290 295 300

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
305 310 315 320

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
325 330 335

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
340 345 350

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
355 360 365

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
370 375 380

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
385 390 395 400

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
405 410 415

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
420 425 430

Gln Ala Leu Pro Pro Arg
435

<210> 216
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 216
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 Gln Gln Ser Gly Pro Glu Leu
            20                  25                  30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220
```

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225 230 235 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
245 250 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp
260 265 270

<210> 217
<211> 267
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 217
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 Gln Gln Ser Gly Pro Asp Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ser Phe Thr Gly Tyr Tyr Met His Trp Val Lys Gln Ser His Gly Lys
50 55 60

Ser Leu Glu Trp Ile Gly Arg Ile Asn Pro Asn Asn Gly Val Thr Leu
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Lys Ala Ile Leu Thr Val Asp Lys Ser
85 90 95

Ser Thr Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Ser Thr Met Ile Thr Asn Tyr Val Met

115 120 125

Asp Tyr Trp Gly Gln Val Thr Ser Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ile Val Met
145 150 155 160

Thr Gln Thr Pro Thr Phe Leu Leu Val Ser Ala Gly Asp Arg Val Thr
165 170 175

Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp Val Ala Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Gln Ser Pro Thr Leu Leu Ile Ser Tyr Thr Ser
195 200 205

Ser Arg Tyr Ala Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Tyr Gly
210 215 220

Thr Asp Phe Thr Phe Thr Ile Ser Thr Leu Gln Ala Glu Asp Leu Ala
225 230 235 240

Val Tyr Phe Cys Gln Gln Asp Tyr Asn Ser Pro Pro Thr Phe Gly Gly
245 250 255

Gly Thr Lys Leu Glu Ile Lys Arg Ser Asp Pro
260 265

<210> 218
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 218
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 Lys Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys
    50                  55                  60

Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

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

Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
145                 150                 155                 160

Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr
                165                 170                 175

Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220
```

Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala
225 230 235 240

Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Leu Glu Ile Thr Arg Ser Asp Pro Thr Ser Ser
260 265 270

<210> 219
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 219
Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr

115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

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

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

Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
180 185 190

Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
195 200 205

Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
210 215 220

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

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
245 250 255

His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
260 265 270

Lys Arg Ser Asp Pro
275

<210> 220
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 220

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

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

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

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205
```

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

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

Ser Ser

<210> 221
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 221
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly

115 120 125

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
130 135 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145 150 155 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
195 200 205

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

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

Ile Lys

<210> 222
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 222
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
        195                 200                 205

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

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240
```

Ile Lys

<210> 223
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 223
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
115 120 125

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

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

145 150 155 160

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
180 185 190

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

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
210 215 220

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

Thr Leu Val Thr Val Ser Ser
245

<210> 224
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 224
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
        115                 120                 125

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
            180                 185                 190

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

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220

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

Thr Leu Val Thr Val Ser Ser
                245
```

<210> 225
<211> 247
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 225

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


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


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


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
    50                  55                  60


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


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


Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160


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


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
```

180 185 190

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

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

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

Gly Thr Lys Leu Glu Ile Lys
245

<210> 226
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 226
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
50 55 60

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

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

```
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160


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


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


Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


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


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


Gly Thr Lys Leu Glu Ile Lys
                245


<210> 227
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 227
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
```

```
1               5                   10                  15

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

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

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gly Gly Gly Gly Ser Gln
        115                 120                 125

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

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160

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

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
            180                 185                 190

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

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
```

210 215 220

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

Thr Leu Val Thr Val Ser Ser
245

<210> 228
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 228
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

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

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

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
50 55 60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

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

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160


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


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


Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


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


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


Gly Thr Lys Leu Glu Ile Lys
                245


<210> 229
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 229
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
```

```
        35                  40                  45

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

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

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu 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 Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

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

Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220

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

Ser Ser
```

<210> 230
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 230
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

```
Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

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

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365
```

```
Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380


Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400


Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415


Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430


Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445


Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460


Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480


Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495


<210> 231
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 231
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


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


Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
```

```
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
    50                  55                  60

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

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

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

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

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

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
        195                 200                 205

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

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

Ile Lys
```

<210> 232
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 232
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 Gly Gly Gly Ser
100 105 110

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

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

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145 150 155 160

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

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

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

Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

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

Ser Ser

<210> 233
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 233
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr

65 70 75 80

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

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
100 105 110

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

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

Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg
145 150 155 160

Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp
165 170 175

Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met
180 185 190

Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
195 200 205

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

Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly
225 230 235 240

Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
245 250

<210> 234
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 234

```
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 Lys Ala Gly Gly Gly
            100                 105                 110

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

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

Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp
145                 150                 155                 160

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

Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu
            180                 185                 190
```

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


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


Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly
225                 230                 235                 240


Gln Gly Thr Ser Val Thr Val Ser Ser Asp
                245                 250


<210> 235
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 235
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 Gly Gly Gly Ser
```

100 105 110

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

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

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145 150 155 160

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

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

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

Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

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

Ser Ser

<210> 236
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 236
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

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

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

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
            100                 105                 110

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

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

Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg
145                 150                 155                 160

Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp
                165                 170                 175

Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met
            180                 185                 190

Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val
    210                 215                 220
```

Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly
225 230 235 240

Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
245 250

<210> 237
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 237
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln

130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser His His His His His His His His
260 265 270

<210> 238
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 238
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu
    130                 135                 140

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

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

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

Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn
        195                 200                 205

Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn Trp Val Phe Gly
225                 230                 235                 240
```

Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 239
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 239
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile

145 150 155 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
165 170 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
180 185 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
195 200 205

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

Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 240
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 240
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

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

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

Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60

```
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
            100                 105                 110

Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
        115                 120                 125

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145                 150                 155                 160

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

Tyr Leu Asn Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Glu Leu Leu
            180                 185                 190

Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Val Gln
    210                 215                 220

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

Leu Thr Phe Gly Pro Gly Thr Lys Val Thr Ile Arg
                245                 250
```

<210> 241
<211> 249
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 241

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160


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


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser
```

180 185 190

Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225 230 235 240

Gly Gln Gly Thr Lys Leu Glu Ile Lys
245

<210> 242
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 242
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145 150 155 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
165 170 175

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

Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
195 200 205

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Asn Arg Asp Trp
225 230 235 240

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 243
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 243
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
```

210 215 220

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 244
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<220>
<221> MOD_RES
<222> (64)..(65)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (68)..(69)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (93)..(93)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (102)..(102)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (104)..(104)
<223> Any amino acid

<220>

<221> MOD_RES
<222> (113)..(113)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (145)..(146)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (148)..(149)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (233)..(233)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (244)..(244)
<223> Any amino acid

<400> 244

```
Gln 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 Gly 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 Xaa
    50                  55                  60


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


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


Ala Xaa Asp Gln Gly Xaa His Xaa Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
```

```
Xaa Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


Xaa Xaa Pro Xaa Xaa Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Val
145                 150                 155                 160


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


Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly
            180                 185                 190


Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


Ser Asp Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln Val Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Ser Ser Xaa Ala Gly Arg Lys Tyr Val Phe
225                 230                 235                 240


Gly Thr Gly Xaa Lys Val Thr Val Leu
                245


<210> 245
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment


<220>
<221> MOD_RES
<222> (76)..(76)
<223> Any amino acid
```

<220>
<221> MOD_RES
<222> (201)..(201)
<223> Any amino acid

<400> 245

```
Gln 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 Gly 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 Xaa Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


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


Ser Cys Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
```

```
Val Thr Val Arg Pro Ser Gly Val Xaa Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 246
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 246
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190


Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205


Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240


Phe Gly Thr Gly Thr Lys Leu Asp Ile Lys
                245                 250


<210> 247
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 247
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
245 250

<210> 248
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 248
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gln Ser Val
115 120 125

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

Ile Ala Cys Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr Asn Tyr Val
145 150 155 160

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
165 170 175

Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
180 185 190

Lys Ser Gly Asn Thr Ala Phe Leu Thr Ile Ser Gly Leu Gln Ala Glu
195 200 205

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

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235

<210> 249
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 249
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Phe
145                 150                 155                 160

Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr Asp His Val Ser
                165                 170                 175

Trp Tyr Gln His His Pro Gly Lys Gly Pro Lys Leu Leu Ile Tyr Asp
            180                 185                 190

Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

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

Glu Ala Asp Tyr Tyr Cys Cys Ser Phe Ala Gly Tyr Tyr Thr Tyr Trp
225                 230                 235                 240

Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250

<210> 250
<211> 246
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 250

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175
```

```
Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190


Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205


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


Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro Phe Gly Gly Gly
225                 230                 235                 240


Thr Lys Leu Thr Val Leu
                245


<210> 251
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 251
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
    130                 135                 140


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


Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp
                165                 170                 175


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


Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205


Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu
    210                 215                 220


Ala Glu Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Asn Val Val
225                 230                 235


<210> 252
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 252
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175

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

Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220
```

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

Phe Gly Gly Gly Thr Lys Val Thr Val Leu
245 250

<210> 253
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 253
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 Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Leu 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 Lys Asn Ser Leu Phe
65 70 75 80

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

Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

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

```
Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160


Ser Cys Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr Thr Ser Val Ser
                165                 170                 175


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


Val Thr Gln Arg Pro Ser Gly Val Pro Asn Arg Phe Ser Gly Ser Lys
        195                 200                 205


Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Asp Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Glu Ala Pro Thr His Thr Tyr
225                 230                 235                 240


Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 254
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 254
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190

Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205

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

Cys Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225                 230                 235                 240

Thr Lys Leu Thr Val Leu
                245
```

<210> 255
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 255

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160


Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr Leu Ala Trp Tyr
                165                 170                 175
```

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


Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240


Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245


<210> 256
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 256
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140


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


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


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


Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205


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


Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240


Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245


<210> 257
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment
```

<400> 257
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115   120   125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130   135   140

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

Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165   170   175

Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180   185   190

Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195   200   205

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


Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 258
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 258
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
```

```
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


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


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


Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190


Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225                 230                 235                 240


Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 259
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 259
Gln 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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175

Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190

Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205

Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240
```

Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 260
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 260
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu
130 135 140

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

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

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

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

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

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

Gly Thr Lys Val Glu Ile Lys
245

<210> 261
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 261
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

```
Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140

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

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

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Phe Asp Ala Ser
            180                 185                 190

Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Met Phe Thr Phe Gly
225                 230                 235                 240

Pro Gly Thr Arg Val Asp Leu Lys
                245
```

<210> 262
<211> 251

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 262
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
130 135 140

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

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Phe Val Ser
165 170 175

```
Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe Leu Ile Tyr Asp
            180                 185                 190


Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp
    210                 215                 220


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


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 263
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 263
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110


Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140


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


Phe Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175


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


Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp
    210                 215                 220


Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Ser Val Val
225                 230                 235                 240


Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 264
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 264
```

```
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

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

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Glu Val Thr Ile
145                 150                 155                 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175

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

Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205
```

Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu Ser Ala Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Val Thr Val Leu
245

<210> 265
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 265
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 Gly 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 Lys Asn Ser Leu Phe
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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
100 105 110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
115 120 125

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ala Val Leu
    130                 135                 140


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


Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175


Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190


Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205


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


Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225                 230                 235                 240


Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250


<210> 266
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      single chain variable fragment

<400> 266
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly 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 Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys 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 Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110

Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140

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

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

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

Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205

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

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240
```

Gly Gln Gly Thr Lys Leu Asp Ile Lys
245

<210> 267
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
single chain variable fragment

<400> 267
Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1 5 10 15

Phe Phe Ala Pro Asp Gly Val Leu Ala Glu Val Gln Leu Gln Gln Ser
20 25 30

Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln
50 55 60

Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn
65 70 75 80

Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
85 90 95

Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr
100 105 110

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Val
115 120 125

Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

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

```
Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro
                165                 170                 175


Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn
            180                 185                 190


Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln
        195                 200                 205


Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val
    210                 215                 220


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


Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Val Cys Met Gln
                245                 250                 255


His Leu Glu Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            260                 265                 270


Lys Arg Ser Asp Pro
        275


<210> 268
<211> 120
<212> PRT
<213> Homo sapiens

<400> 268
Trp Arg Arg Lys Arg Lys Glu Lys Gln Ser Glu Thr Ser Pro Lys Glu
1               5                   10                  15


Phe Leu Thr Ile Tyr Glu Asp Val Lys Asp Leu Lys Thr Arg Arg Asn
            20                  25                  30


His Glu Gln Glu Gln Thr Phe Pro Gly Gly Gly Ser Thr Ile Tyr Ser
        35                  40                  45
```

Met Ile Gln Ser Gln Ser Ser Ala Pro Thr Ser Gln Glu Pro Ala Tyr
50 55 60

Thr Leu Tyr Ser Leu Ile Gln Pro Ser Arg Lys Ser Gly Ser Arg Lys
65 70 75 80

Arg Asn His Ser Pro Ser Phe Asn Ser Thr Ile Tyr Glu Val Ile Gly
85 90 95

Lys Ser Gln Pro Lys Ala Gln Asn Pro Ala Arg Leu Ser Arg Lys Glu
100 105 110

Leu Glu Asn Phe Asp Val Tyr Ser
115 120

<210> 269
<211> 49
<212> PRT
<213> Homo sapiens

<400> 269
His Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu
1 5 10 15

Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser
20 25 30

Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser
35 40 45

Pro

<210> 270
<211> 110
<212> PRT
<213> Homo sapiens

<400> 270
Arg Arg His Gln Gly Lys Gln Asn Glu Leu Ser Asp Thr Ala Gly Arg
1 5 10 15

```
Glu Ile Asn Leu Val Asp Ala Lys Leu Lys Ser Glu Gln Thr Glu Ala
            20                  25                  30

Ser Thr Arg Gln Asn Ser Gln Val Leu Leu Ser Glu Thr Gly Ile Tyr
        35                  40                  45

Asp Asn Asp Pro Asp Leu Cys Phe Arg Met Gln Glu Gly Ser Glu Val
    50                  55                  60

Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys Pro Gly Val Tyr Ala Ser
65                  70                  75                  80

Leu Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu Ala Arg Asn Val
                85                  90                  95

Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val Arg Ser
            100                 105                 110
```

<210> 271
<211> 114
<212> PRT
<213> Homo sapiens

<400> 271

```
Cys Cys Leu Arg Arg His Gln Gly Lys Gln Asn Glu Leu Ser Asp Thr
1               5                   10                  15

Ala Gly Arg Glu Ile Asn Leu Val Asp Ala His Leu Lys Ser Glu Gln
            20                  25                  30

Thr Glu Ala Ser Thr Arg Gln Asn Ser Gln Val Leu Leu Ser Glu Thr
        35                  40                  45

Gly Ile Tyr Asp Asn Asp Pro Asp Leu Cys Phe Arg Met Gln Glu Gly
    50                  55                  60

Ser Glu Val Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys Pro Gly Ile
65                  70                  75                  80

Val Tyr Ala Ser Leu Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu
                85                  90                  95
```

Ala Arg Asn Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val
100 105 110

Arg Ser

<210> 272
<211> 27
<212> PRT
<213> Homo sapiens

<400> 272
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> 273
<211> 42
<212> PRT
<213> Homo sapiens

<400> 273
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> 274
<211> 44
<212> PRT
<213> Homo sapiens

<400> 274
Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
1 5 10 15

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
20 25 30

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 275
<211> 41
<212> PRT
<213> Homo sapiens

<400> 275
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 276
<211> 43
<212> PRT
<213> Homo sapiens

<400> 276
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Ile Val Ile Asn
1 5 10 15

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
20 25 30

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 277
<211> 220
<212> PRT
<213> Homo sapiens

<400> 277
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1 5 10 15

```
Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
        35                  40                  45

Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
    50                  55                  60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65                  70                  75                  80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
                85                  90                  95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145                 150                 155                 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                165                 170                 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            180                 185                 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        195                 200                 205

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
    210                 215                 220
```

<210> 278
<211> 187
<212> PRT
<213> Homo sapiens

<400> 278
Arg Arg Ala Cys Arg Lys Arg Ile Arg Gln Lys Leu His Leu Cys Tyr
1   5   10   15

Pro Val Gln Thr Ser Gln Pro Lys Leu Glu Leu Val Asp Ser Arg Pro
            20   25   30

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

Val Ala Glu Glu Arg Gly Leu Met Ser Gln Pro Leu Met Glu Thr Cys
    50   55   60

His Ser Val Gly Ala Ala Tyr Leu Glu Ser Leu Pro Leu Gln Asp Ala
65   70   75   80

Ser Pro Ala Gly Gly Pro Ser Ser Pro Arg Asp Leu Pro Glu Pro Arg
                85   90   95

Val Ser Thr Glu His Thr Asn Asn Lys Ile Glu Lys Ile Tyr Ile Met
            100   105   110

Lys Ala Asp Thr Val Ile Val Gly Thr Val Lys Ala Glu Leu Pro Glu
        115   120   125

Gly Arg Gly Leu Ala Gly Pro Ala Glu Pro Glu Leu Glu Glu Glu Leu
    130   135   140

Glu Ala Asp His Thr Pro His Tyr Pro Glu Gln Glu Thr Glu Pro Pro
145   150   155   160

Leu Gly Ser Cys Ser Asp Val Met Leu Ser Val Glu Glu Glu Gly Lys
                165   170   175

Glu Asp Pro Leu Pro Thr Ala Ala Ser Gly Lys
180 185

<210> 279
<211> 187
<212> PRT
<213> Homo sapiens

<400> 279
Arg Arg Ala Cys Arg Lys Arg Ile Arg Gln Lys Leu His Leu Cys Tyr
1 5 10 15

Pro Val Gln Thr Ser Gln Pro Lys Leu Glu Leu Val Asp Ser Arg Pro
20 25 30

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

Val Ala Glu Glu Arg Gly Leu Met Ser Gln Pro Leu Met Glu Thr Cys
50 55 60

His Ser Val Gly Ala Ala Tyr Leu Glu Ser Leu Pro Leu Gln Asp Ala
65 70 75 80

Ser Pro Ala Gly Gly Pro Ser Ser Pro Arg Asp Leu Pro Glu Pro Arg
85 90 95

Val Ser Thr Glu His Thr Asn Asn Lys Ile Glu Lys Ile Tyr Ile Met
100 105 110

Lys Ala Asp Thr Val Ile Val Gly Thr Val Lys Ala Glu Leu Pro Glu
115 120 125

Gly Arg Gly Leu Ala Gly Pro Ala Glu Pro Glu Leu Glu Glu Glu Leu
130 135 140

Glu Ala Asp His Thr Pro His Tyr Pro Glu Gln Glu Thr Glu Pro Pro
145 150 155 160

Leu Gly Ser Cys Ser Asp Val Met Leu Ser Val Glu Glu Glu Gly Lys
165 170 175

Glu Asp Pro Leu Pro Thr Ala Ala Ser Gly Lys
180 185

<210> 280
<211> 54
<212> PRT
<213> Homo sapiens

<400> 280
His Ile Trp Gln Leu Arg Ser Gln Cys Met Trp Pro Arg Glu Thr Gln
1 5 10 15

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

Phe Pro Glu Glu Glu Arg Gly Glu Arg Ser Ala Glu Glu Lys Gly Arg
35 40 45

Leu Gly Asp Leu Trp Val
50

<210> 281
<211> 60
<212> PRT
<213> Homo sapiens

<400> 281
Cys Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile Val
1 5 10 15

Ser Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val Ile
20 25 30

Glu Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu Glu
35 40 45

Thr Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His
50 55 60

<210> 282
<211> 35

<212> PRT
<213> Homo sapiens

<400> 282
Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn Gly Glu Tyr
1 5 10 15

Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg Leu Thr Asp
            20 25 30

Val Thr Leu
        35

<210> 283
<211> 38
<212> PRT
<213> Homo sapiens

<400> 283
Cys Trp Leu Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn
1 5 10 15

Gly Glu Tyr Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg
            20 25 30

Leu Thr Asp Val Thr Leu
        35

<210> 284
<211> 54
<212> PRT
<213> Homo sapiens

<400> 284
His Leu Trp Arg Arg Gln Trp Arg Pro Arg Arg Phe Ser Ala Leu Glu
1 5 10 15

Gln Gly Ile His Pro Pro Gln Ala Gln Ser Lys Ile Glu Glu Leu Glu
            20 25 30

Gln Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu
        35 40 45

Pro Glu Pro Glu Gln Leu
    50

<210> 285
<211> 42
<212> PRT
<213> Homo sapiens

<400> 285
Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His
1   5   10   15

Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln
            20   25   30

Ala Asp Ala His Ser Thr Leu Ala Lys Ile
        35   40

<210> 286
<211> 37
<212> PRT
<213> Homo sapiens

<400> 286
Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
1   5   10   15

Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
            20   25   30

Thr Leu Ala Lys Ile
        35

<210> 287
<211> 42
<212> PRT
<213> Homo sapiens

<400> 287
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 Ile 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> 288
<211> 42
<212> PRT
<213> Homo sapiens

<400> 288
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 Tyr Glu Leu
        35   40

<210> 289
<211> 225
<212> PRT
<213> Homo sapiens

<400> 289
Thr Gly Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
1   5   10   15

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

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

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
    50   55   60

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
65   70   75   80

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
                85   90   95

```
Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
            100                 105                 110

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
        115                 120                 125

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
    130                 135                 140

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
145                 150                 155                 160

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
                165                 170                 175

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
            180                 185                 190

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
        195                 200                 205

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
    210                 215                 220

Arg
225


<210> 290
<211> 154
<212> PRT
<213> Homo sapiens

<400> 290
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 Arg Val Lys Phe Ser Arg
        35                  40                  45

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
    50                  55                  60

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
65                  70                  75                  80

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                85                  90                  95

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            100                 105                 110

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        115                 120                 125

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    130                 135                 140

Ala Leu His Met Gln Ala Leu Pro Pro Arg
145                 150
```

<210> 291
<211> 194
<212> PRT
<213> Homo sapiens

<400> 291

```
Lys Arg Ile Lys Pro Ile Val Trp Pro Ser Leu Pro Asp His Lys Lys
1               5                   10                  15

Thr Leu Glu His Leu Cys Lys Lys Pro Arg Lys Asn Leu Asn Val Ser
            20                  25                  30

Phe Asn Pro Glu Ser Phe Leu Asp Cys Gln Ile His Arg Val Asp Asp
        35                  40                  45

Ile Gln Ala Arg Asp Glu Val Glu Gly Phe Leu Gln Asp Thr Phe Pro
    50                  55                  60
```

```
Gln Gln Leu Glu Glu Ser Glu Lys Gln Arg Leu Gly Gly Asp Val Gln
65                  70                  75                  80


Ser Pro Asn Cys Pro Ser Glu Asp Val Val Ile Thr Pro Glu Ser Phe
                85                  90                  95


Gly Arg Asp Ser Ser Leu Thr Cys Leu Ala Gly Asn Val Ser Ala Cys
            100                 105                 110


Asp Ala Pro Ile Leu Ser Ser Ser Arg Ser Leu Asp Cys Arg Glu Ser
        115                 120                 125


Gly Lys Asn Gly Pro His Val Tyr Gln Asp Leu Leu Leu Ser Leu Gly
    130                 135                 140


Thr Thr Asn Ser Thr Leu Pro Pro Pro Phe Ser Leu Gln Ser Gly Ile
145                 150                 155                 160


Leu Thr Leu Asn Pro Val Ala Gln Gly Gln Pro Ile Leu Thr Ser Leu
                165                 170                 175


Gly Ser Asn Gln Glu Glu Ala Tyr Val Thr Met Ser Ser Phe Tyr Gln
            180                 185                 190


Asn Gln



<210> 292
<211> 47
<212> PRT
<213> Homo sapiens

<400> 292
Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
1               5                   10                  15


Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
            20                  25                  30
```

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40 45

<210> 293
<211> 341
<212> PRT
<213> Homo sapiens

<400> 293
Arg Lys Lys Arg Lys Asp Ala Lys Asn Asn Glu Val Ser Phe Ser Gln
1 5 10 15

Ile Lys Pro Lys Lys Ser Lys Leu Ile Arg Val Glu Asn Phe Glu Ala
20 25 30

Tyr Phe Lys Lys Gln Gln Ala Asp Ser Asn Cys Gly Phe Ala Glu Glu
35 40 45

Tyr Glu Asp Leu Lys Leu Val Gly Ile Ser Gln Pro Lys Tyr Ala Ala
50 55 60

Glu Leu Ala Glu Asn Arg Gly Lys Asn Arg Tyr Asn Asn Val Leu Pro
65 70 75 80

Tyr Asp Ile Ser Arg Val Lys Leu Ser Val Gln Thr His Ser Thr Asp
85 90 95

Asp Tyr Ile Asn Ala Asn Tyr Met Pro Gly Tyr His Ser Lys Lys Asp
100 105 110

Phe Ile Ala Thr Gln Gly Pro Leu Pro Asn Thr Leu Lys Asp Phe Trp
115 120 125

Arg Met Val Trp Glu Lys Asn Val Tyr Ala Ile Ile Met Leu Thr Lys
130 135 140

Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu Tyr Trp Pro Ser Lys
145 150 155 160

Gln Ala Gln Asp Tyr Gly Asp Ile Thr Val Ala Met Thr Ser Glu Ile
165 170 175

```
Val Leu Pro Glu Trp Thr Ile Arg Asp Phe Thr Val Lys Asn Ile Gln
            180                 185                 190

Thr Ser Glu Ser His Pro Leu Arg Gln Phe His Phe Thr Ser Trp Pro
        195                 200                 205

Asp His Gly Val Pro Asp Thr Thr Asp Leu Leu Ile Asn Phe Arg Tyr
    210                 215                 220

Leu Val Arg Asp Tyr Met Lys Gln Ser Pro Pro Glu Ser Pro Ile Leu
225                 230                 235                 240

Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala Ile
                245                 250                 255

Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu Asn Thr Val Asp Val Tyr
            260                 265                 270

Gly Ile Val Tyr Asp Leu Arg Met His Arg Pro Leu Met Val Gln Thr
        275                 280                 285

Glu Asp Gln Tyr Val Phe Leu Asn Gln Cys Val Leu Asp Ile Val Arg
    290                 295                 300

Ser Gln Lys Asp Ser Lys Val Asp Leu Ile Tyr Gln Asn Thr Thr Ala
305                 310                 315                 320

Met Thr Ile Tyr Glu Asn Leu Ala Pro Val Thr Thr Phe Gly Lys Thr
                325                 330                 335

Asn Gly Tyr Ile Ala
            340
```

<210> 294
<211> 48
<212> PRT
<213> Homo sapiens

<400> 294

Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro
1 5 10 15

Ala Glu Pro Cys His Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr
20 25 30

Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro
35 40 45

<210> 295
<211> 6
<212> PRT
<213> Homo sapiens

<400> 295
Phe Ala Ala Tyr Arg Ser
1 5

<210> 296
<211> 68
<212> PRT
<213> Homo sapiens

<400> 296
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
20 25 30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
35 40 45

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
50 55 60

Ala Tyr Arg Ser
65

<210> 297
<211> 41
<212> PRT
<213> Homo sapiens

<400> 297
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1   5   10   15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20   25   30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35   40

<210> 298
<211> 40
<212> PRT
<213> Homo sapiens

<400> 298
Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
1   5   10   15

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
            20   25   30

Arg Asp Phe Ala Ala Tyr Arg Ser
        35   40

<210> 299
<211> 106
<212> PRT
<213> Homo sapiens

<400> 299
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1   5   10   15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
            20   25   30

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

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
    50   55   60

```
Trp Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
65                  70                  75                  80


Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
                85                  90                  95


Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            100                 105


<210> 300
<211> 200
<212> PRT
<213> Homo sapiens

<400> 300
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1               5                   10                  15


Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30


Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
        35                  40                  45


Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
    50                  55                  60


Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
65                  70                  75                  80


Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
                85                  90                  95


Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
            100                 105                 110


Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
        115                 120                 125
```

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
130 135 140

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
145 150 155 160

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
165 170 175

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
180 185 190

His Met Gln Ala Leu Pro Pro Arg
195 200

<210> 301
<211> 222
<212> PRT
<213> Homo sapiens

<400> 301
Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu
1 5 10 15

Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro
20 25 30

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

Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe
50 55 60

Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp
65 70 75 80

Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr
85 90 95

Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val
100 105 110

```
Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
        115                 120                 125


Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
    130                 135                 140


Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
145                 150                 155                 160


Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
                165                 170                 175


Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
            180                 185                 190


Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
        195                 200                 205


Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    210                 215                 220


<210> 302
<211> 188
<212> PRT
<213> Homo sapiens

<400> 302
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Asn Met Thr Pro
1               5                   10                  15


Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
            20                  25                  30


Arg Asp Phe Ala Ala Tyr Arg Ser Arg Asp Gln Arg Leu Pro Pro Asp
        35                  40                  45


Ala His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu
    50                  55                  60
```

```
Glu Gln Ala Asp Ala His Ser Thr Leu Ala Lys Ile Arg Val Lys Phe
65                  70                  75                  80


Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
                85                  90                  95


Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
            100                 105                 110


Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
        115                 120                 125


Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
    130                 135                 140


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
145                 150                 155                 160


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
                165                 170                 175


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            180                 185


<210> 303
<211> 70
<212> PRT
<213> Homo sapiens

<400> 303
Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1               5                   10                  15


Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly Arg
            20                  25                  30


Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
        35                  40                  45


Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
    50                  55                  60
```

Glu Gly Gly Cys Glu Leu
65 70

<210> 304
<211> 108
<212> PRT
<213> Homo sapiens

<400> 304
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1 5 10 15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
20 25 30

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

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
50 55 60

Trp Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
65 70 75 80

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
85 90 95

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
100 105

<210> 305
<211> 153
<212> PRT
<213> Homo sapiens

<400> 305
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

```
Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
        35                  40                  45


Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
    50                  55                  60


Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
65                  70                  75                  80


Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
                85                  90                  95


Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
            100                 105                 110


Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
        115                 120                 125


Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
    130                 135                 140


Leu His Met Gln Ala Leu Pro Pro Arg
145                 150


<210> 306
<211> 151
<212> PRT
<213> Homo sapiens

<400> 306
Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
1               5                   10                  15


Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
            20                  25                  30


Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
        35                  40                  45
```

```
Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
    50                  55                  60

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
65                  70                  75                  80

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
                85                  90                  95

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
            100                 105                 110

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
        115                 120                 125

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
    130                 135                 140

Met Gln Ala Leu Pro Pro Arg
145                 150
```

<210> 307
<211> 171
<212> PRT
<213> Homo sapiens

<400> 307

```
Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1               5                   10                  15

Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
            20                  25                  30

Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
        35                  40                  45

Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
    50                  55                  60

Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65                  70                  75                  80
```

```
Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Met Cys Gln Ser Cys
                85                  90                  95


Val Glu Leu Asp Pro Ala Thr Val Ala Gly Ile Ile Val Thr Asp Val
            100                 105                 110


Ile Ala Thr Leu Leu Leu Ala Leu Gly Val Phe Cys Phe Ala Gly His
        115                 120                 125


Glu Thr Gly Arg Leu Ser Gly Ala Ala Asp Thr Gln Ala Leu Leu Arg
    130                 135                 140


Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr
145                 150                 155                 160


Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
                165                 170


<210> 308
<211> 127
<212> PRT
<213> Homo sapiens

<400> 308
Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1               5                   10                  15


Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
            20                  25                  30


Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
        35                  40                  45


Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
    50                  55                  60


Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65                  70                  75                  80
```

```
Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Thr Ala Asp Thr Gln
                85                  90                  95


Ala Leu Leu Arg Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp
            100                 105                 110


Asp Ala Gln Tyr Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
        115                 120                 125


<210> 309
<211> 21
<212> PRT
<213> Homo sapiens

<400> 309
Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr Ser
1               5                   10                  15


His Leu Gly Gly Asn
            20


<210> 310
<211> 171
<212> PRT
<213> Homo sapiens

<400> 310
Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1               5                   10                  15


Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
            20                  25                  30


Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
        35                  40                  45


Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
    50                  55                  60


Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65                  70                  75                  80
```

Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Met Cys Gln Ser Cys
85 90 95

Val Glu Leu Asp Pro Ala Thr Val Ala Gly Ile Ile Val Thr Asp Val
100 105 110

Ile Ala Thr Leu Leu Leu Ala Leu Gly Val Phe Cys Phe Ala Gly His
115 120 125

Glu Thr Gly Arg Leu Ser Gly Ala Ala Asp Thr Gln Ala Leu Leu Arg
130 135 140

Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr
145 150 155 160

Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
165 170

<210> 311
<211> 127
<212> PRT
<213> Homo sapiens

<400> 311
Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1 5 10 15

Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
20 25 30

Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
35 40 45

Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
50 55 60

Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65 70 75 80

Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Thr Ala Asp Thr Gln
85 90 95

```
Ala Leu Leu Arg Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp
            100                 105                 110


Asp Ala Gln Tyr Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
        115                 120                 125


<210> 312
<211> 21
<212> PRT
<213> Homo sapiens

<400> 312
Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr Ser
1               5                   10                  15


His Leu Gly Gly Asn
            20


<210> 313
<211> 207
<212> PRT
<213> Homo sapiens

<400> 313
Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1               5                   10                  15


Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
            20                  25                  30


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


Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
    50                  55                  60


Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65                  70                  75                  80


His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
                85                  90                  95
```

```
Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
            100                 105                 110


Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
        115                 120                 125


Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
    130                 135                 140


Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145                 150                 155                 160


Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
                165                 170                 175


Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
            180                 185                 190


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


<210> 314
<211> 21
<212> PRT
<213> Homo sapiens

<400> 314
Asn Pro Asp Tyr Glu Pro Ile Arg Lys Gly Gln Arg Asp Leu Tyr Ser
1               5                   10                  15


Gly Leu Asn Gln Arg
            20


<210> 315
<211> 182
<212> PRT
<213> Homo sapiens

<400> 315
Met Glu Gln Gly Lys Gly Leu Ala Val Leu Ile Leu Ala Ile Ile Leu
1               5                   10                  15
```

```
Leu Gln Gly Thr Leu Ala Gln Ser Ile Lys Gly Asn His Leu Val Lys
            20                  25                  30

Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu Leu Thr Cys Asp Ala
        35                  40                  45

Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly Lys Met Ile Gly Phe
    50                  55                  60

Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly Ser Asn Ala Lys Asp
65                  70                  75                  80

Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln Asn Lys Ser Lys Pro
                85                  90                  95

Leu Gln Val Tyr Tyr Arg Met Cys Gln Asn Cys Ile Glu Leu Asn Ala
            100                 105                 110

Ala Thr Ile Ser Gly Phe Leu Phe Ala Glu Ile Val Ser Ile Phe Val
        115                 120                 125

Leu Ala Val Gly Val Tyr Phe Ile Ala Gly Gln Asp Gly Val Arg Gln
    130                 135                 140

Ser Arg Ala Ser Asp Lys Gln Thr Leu Leu Pro Asn Asp Gln Leu Tyr
145                 150                 155                 160

Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser His Leu Gln Gly
                165                 170                 175

Asn Gln Leu Arg Arg Asn
            180
```

<210> 316
<211> 21
<212> PRT
<213> Homo sapiens

<400> 316

```
Asp Gln Leu Tyr Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser
1               5                   10                  15


His Leu Gln Gly Asn
            20


<210> 317
<211> 21
<212> PRT
<213> Homo sapiens

<400> 317
Asp Gln Leu Tyr Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser
1               5                   10                  15


His Leu Gln Gly Asn
            20


<210> 318
<211> 182
<212> PRT
<213> Homo sapiens

<400> 318
Met Glu Gln Gly Lys Gly Leu Ala Val Leu Ile Leu Ala Ile Ile Leu
1               5                   10                  15


Leu Gln Gly Thr Leu Ala Gln Ser Ile Lys Gly Asn His Leu Val Lys
            20                  25                  30


Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu Leu Thr Cys Asp Ala
        35                  40                  45


Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly Lys Met Ile Gly Phe
    50                  55                  60


Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly Ser Asn Ala Lys Asp
65                  70                  75                  80


Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln Asn Lys Ser Lys Pro
                85                  90                  95
```

```
Leu Gln Val Tyr Tyr Arg Met Cys Gln Asn Cys Ile Glu Leu Asn Ala
            100                 105                 110


Ala Thr Ile Ser Gly Phe Leu Phe Ala Glu Ile Val Ser Ile Phe Val
        115                 120                 125


Leu Ala Val Gly Val Tyr Phe Ile Ala Gly Gln Asp Gly Val Arg Gln
    130                 135                 140


Ser Arg Ala Ser Asp Lys Gln Thr Leu Leu Pro Asn Asp Gln Leu Tyr
145                 150                 155                 160


Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser His Leu Gln Gly
                165                 170                 175


Asn Gln Leu Arg Arg Asn
            180


<210> 319
<211> 163
<212> PRT
<213> Homo sapiens

<400> 319
Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1               5                   10                  15


Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
            20                  25                  30


Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
        35                  40                  45


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


Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65                  70                  75                  80


Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                85                  90                  95
```

```
Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            100                 105                 110

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        115                 120                 125

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    130                 135                 140

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
145                 150                 155                 160

Pro Pro Arg
```

<210> 320
<211> 164
<212> PRT
<213> Homo sapiens

<400> 320

```
Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1               5                   10                  15

Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
            20                  25                  30

Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
        35                  40                  45

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

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65                  70                  75                  80

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                85                  90                  95
```

Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
100 105 110

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
115 120 125

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
130 135 140

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
145 150 155 160

Leu Pro Pro Arg

<210> 321
<211> 164
<212> PRT
<213> Homo sapiens

<400> 321
Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1 5 10 15

Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
20 25 30

Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
35 40 45

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

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65 70 75 80

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
85 90 95

Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
100 105 110

```
Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        115                 120                 125


Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    130                 135                 140


Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
145                 150                 155                 160


Leu Pro Pro Arg



<210> 322
<211> 21
<212> PRT
<213> Homo sapiens

<400> 322
Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
1               5                   10                  15


Val Leu Asp Lys Arg
            20



<210> 323
<211> 112
<212> PRT
<213> Homo sapiens

<400> 323
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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> 324
<211> 21
<212> PRT
<213> Homo sapiens

<400> 324
Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
1               5                   10                  15


Ala Leu His Met Gln
            20


<210> 325
<211> 112
<212> PRT
<213> Homo sapiens

<400> 325
Arg Val Lys Phe Ser Arg Ser Ala Glu Pro Pro Ala Tyr Gln 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> 326
<211> 113
<212> PRT
<213> Homo sapiens

<400> 326
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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 Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
    50                  55                  60

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

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

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

Arg


<210> 327
<211> 114
<212> PRT
<213> Homo sapiens
```

<400> 327
Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
1   5   10   15

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

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

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

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

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

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

Pro Arg

<210> 328
<211> 98
<212> PRT
<213> Homo sapiens

<400> 328
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1   5   10   15

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
            20   25   30

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        35   40   45

```
Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    50                  55                  60

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
65                  70                  75                  80

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                85                  90                  95

Pro Arg
```

<210> 329
<211> 112
<212> PRT
<213> Homo sapiens

<400> 329

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

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Val
            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> 330
<211> 173

<212> PRT
<213> Homo sapiens

<400> 330
Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Val Glu Gln Ala
1   5   10   15

Ala Ala Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu
            20   25   30

Phe Leu Val Gly Ile Val Leu Thr Leu Leu Val Cys Arg Leu Lys Ile
        35   40   45

Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser Arg Val Lys
    50   55   60

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
65   70   75   80

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                85   90   95

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            100   105   110

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        115   120   125

Ala Glu Ala Val Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    130   135   140

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
145   150   155   160

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                165   170

<210> 331
<211> 113
<212> PRT
<213> Homo sapiens

<400> 331
Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
1   5   10   15

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

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

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

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

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

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

Arg

<210> 332
<211> 60
<212> PRT
<213> Homo sapiens

<400> 332
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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 Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
50 55 60

<210> 333
<211> 114
<212> PRT
<213> Homo sapiens

<400> 333
Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
1 5 10 15

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

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

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

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

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

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

Pro Arg

<210> 334
<211> 113
<212> PRT
<213> Homo sapiens

<400> 334
Arg Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
1 5 10 15

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

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

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

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

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

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

Arg

<210> 335
<211> 21
<212> PRT
<213> Homo sapiens

<400> 335
Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
1   5   10   15

Val Leu Asp Lys Arg
            20

<210> 336
<211> 22
<212> PRT
<213> Homo sapiens

<400> 336
Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
1   5   10   15

Ser Glu Ile Gly Met Lys
            20

<210> 337
<211> 21
<212> PRT
<213> Homo sapiens

<400> 337
Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
1   5   10   15

Ala Leu His Met Gln
            20

<210> 338
<211> 112
<212> PRT
<213> Homo sapiens

<400> 338
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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> 339
<211> 112
<212> PRT
<213> Homo sapiens

<400> 339
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> 340
<211> 110
<212> PRT
<213> Homo sapiens

<400> 340
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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
            100                 105                 110
```

<210> 341
<211> 137
<212> PRT
<213> Homo sapiens

<400> 341

```
Asp Pro Lys Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly
1               5                   10                  15

Val Ile Leu Thr Ala Leu Phe Leu Arg Val Lys Phe Ser Arg Ser Ala
            20                  25                  30

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
        35                  40                  45

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
    50                  55                  60

Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln
65                  70                  75                  80

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
                85                  90                  95

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
            100                 105                 110

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
        115                 120                 125
```

Leu His Met Gln Ala Leu Pro Pro Arg
130 135

<210> 342
<211> 163
<212> PRT
<213> Homo sapiens

<400> 342
Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1 5 10 15

Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
20 25 30

Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
35 40 45

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

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65 70 75 80

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
85 90 95

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
100 105 110

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
115 120 125

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
130 135 140

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
145 150 155 160

Pro Pro Arg

<210> 343
<211> 38
<212> PRT
<213> Homo sapiens

<400> 343
Arg Ser Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly
1 5 10 15

Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His
20 25 30

Ser Thr Leu Ala Lys Ile
35

<210> 344
<211> 226
<212> PRT
<213> Homo sapiens

<400> 344
Met Pro Gly Gly Pro Gly Val Leu Gln Ala Leu Pro Ala Thr Ile Phe
1 5 10 15

Leu Leu Phe Leu Leu Ser Ala Val Tyr Leu Gly Pro Gly Cys Gln Ala
20 25 30

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

Asp Ala His Phe Gln Cys Pro His Asn Ser Ser Asn Asn Ala Asn Val
50 55 60

Thr Trp Trp Arg Val Leu His Gly Asn Tyr Thr Trp Pro Pro Glu Phe
65 70 75 80

Leu Gly Pro Gly Glu Asp Pro Asn Gly Thr Leu Ile Ile Gln Asn Val
85 90 95

```
Asn Lys Ser His Gly Gly Ile Tyr Val Cys Arg Val Gln Glu Gly Asn
            100                 105                 110

Glu Ser Tyr Gln Gln Ser Cys Gly Thr Tyr Leu Arg Val Arg Gln Pro
        115                 120                 125

Pro Pro Arg Pro Phe Leu Asp Met Gly Glu Gly Thr Lys Asn Arg Ile
    130                 135                 140

Ile Thr Ala Glu Gly Ile Ile Leu Leu Phe Cys Ala Val Val Pro Gly
145                 150                 155                 160

Thr Leu Leu Leu Phe Arg Lys Arg Trp Gln Asn Glu Lys Leu Gly Leu
                165                 170                 175

Asp Ala Gly Asp Glu Tyr Glu Asp Glu Asn Leu Tyr Glu Gly Leu Asn
            180                 185                 190

Leu Asp Asp Cys Ser Met Tyr Glu Asp Ile Ser Arg Gly Leu Gln Gly
        195                 200                 205

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

Lys Pro
225
```

<210> 345
<211> 188
<212> PRT
<213> Homo sapiens

<400> 345

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

Leu Leu Phe Leu Leu Ser Ala Val Tyr Leu Gly Pro Gly Cys Gln Ala
            20                  25                  30

Leu Trp Met His Lys Val Pro Ala Ser Leu Met Val Ser Leu Gly Glu
        35                  40                  45
```

```
Asp Ala His Phe Gln Cys Pro His Asn Ser Ser Asn Asn Ala Asn Val
    50                  55                  60

Thr Trp Trp Arg Val Leu His Gly Asn Tyr Thr Trp Pro Pro Glu Phe
65                  70                  75                  80

Leu Gly Pro Gly Glu Asp Pro Asn Glu Pro Pro Pro Arg Pro Phe Leu
                85                  90                  95

Asp Met Gly Glu Gly Thr Lys Asn Arg Ile Ile Thr Ala Glu Gly Ile
            100                 105                 110

Ile Leu Leu Phe Cys Ala Val Val Pro Gly Thr Leu Leu Leu Phe Arg
        115                 120                 125

Lys Arg Trp Gln Asn Glu Lys Leu Gly Leu Asp Ala Gly Asp Glu Tyr
    130                 135                 140

Glu Asp Glu Asn Leu Tyr Glu Gly Leu Asn Leu Asp Asp Cys Ser Met
145                 150                 155                 160

Tyr Glu Asp Ile Ser Arg Gly Leu Gln Gly Thr Tyr Gln Asp Val Gly
                165                 170                 175

Ser Leu Asn Ile Gly Asp Val Gln Leu Glu Lys Pro
            180                 185


<210> 346
<211> 226
<212> PRT
<213> Homo sapiens

<400> 346
Met Pro Gly Gly Pro Gly Val Leu Gln Ala Leu Pro Ala Thr Ile Phe
1               5                   10                  15

Leu Leu Phe Leu Leu Ser Ala Val Tyr Leu Gly Pro Gly Cys Gln Ala
            20                  25                  30
```

```
Leu Trp Met His Lys Val Pro Ala Ser Leu Met Val Ser Leu Gly Glu
        35                  40                  45

Asp Ala His Phe Gln Cys Pro His Asn Ser Ser Asn Asn Ala Asn Val
    50                  55                  60

Thr Trp Trp Arg Val Leu His Gly Asn Tyr Thr Trp Pro Pro Glu Phe
65                  70                  75                  80

Leu Gly Pro Gly Glu Asp Pro Asn Gly Thr Leu Ile Ile Gln Asn Val
                85                  90                  95

Asn Lys Ser His Gly Gly Ile Tyr Val Cys Arg Val Gln Glu Gly Asn
            100                 105                 110

Glu Ser Tyr Gln Gln Ser Cys Gly Thr Tyr Leu Arg Val Arg Gln Pro
        115                 120                 125

Pro Pro Arg Pro Phe Leu Asp Met Gly Glu Gly Thr Lys Asn Arg Ile
    130                 135                 140

Ile Thr Ala Glu Gly Ile Ile Leu Leu Phe Cys Ala Val Val Pro Gly
145                 150                 155                 160

Thr Leu Leu Leu Phe Arg Lys Arg Trp Gln Asn Glu Lys Leu Gly Leu
                165                 170                 175

Asp Ala Gly Asp Glu Tyr Glu Asp Glu Asn Leu Tyr Glu Gly Leu Asn
            180                 185                 190

Leu Asp Asp Cys Ser Met Tyr Glu Asp Ile Ser Arg Gly Leu Gln Gly
        195                 200                 205

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

Lys Pro
225
```

<210> 347
<211> 21
<212> PRT
<213> Homo sapiens

<400> 347
Glu Asn Leu Tyr Glu Gly Leu Asn Leu Asp Asp Cys Ser Met Tyr Glu
1 5 10 15

Asp Ile Ser Arg Gly
            20

<210> 348
<211> 84
<212> PRT
<213> Homo sapiens

<400> 348
Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
1 5 10 15

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            20 25 30

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        35 40 45

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    50 55 60

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
65 70 75 80

His Arg Asn Arg

<210> 349
<211> 84
<212> PRT
<213> Homo sapiens

<400> 349
Phe Val Pro Val Phe Leu Pro Ala Lys Pro Ile Thr Thr Pro Ala Pro
1 5 10 15

```
Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            20                  25                  30

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        35                  40                  45

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    50                  55                  60

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
65                  70                  75                  80

His Arg Asn Arg
```

<210> 350
<211> 47
<212> PRT
<213> Homo sapiens

<400> 350

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

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

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

<210> 351
<211> 41
<212> PRT
<213> Homo sapiens

<400> 351

```
Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr
1               5                   10                  15

Gly Val Phe Val Lys Met Ala Pro Thr Glu Ala Glu Cys Glu Lys Gln
            20                  25                  30
```

Phe Gln Pro Tyr Phe Ile Pro Ile Asn
        35   40

<210> 352
<211> 47
<212> PRT
<213> Homo sapiens

<400> 352
Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr
1   5   10   15

Gly Val Tyr Met Asn Met Thr Pro Arg Arg Pro Glu Cys Glu Lys Gln
            20   25   30

Phe Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35   40   45

<210> 353
<211> 20
<212> PRT
<213> Homo sapiens

<400> 353
Arg Pro Arg Arg Ser Pro Ala Gln Asp Gly Lys Val Tyr Ile Asn Met
1   5   10   15

Pro Gly Arg Gly
            20

<210> 354
<211> 113
<212> PRT
<213> Homo sapiens

<400> 354
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1   5   10   15

Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
            20   25   30

Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
35 40 45

Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
50 55 60

Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Ala Thr Arg
65 70 75 80

Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly
85 90 95

Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr
100 105 110

Lys

<210> 355
<211> 112
<212> PRT
<213> Homo sapiens

<400> 355
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1 5 10 15

Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
20 25 30

Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
35 40 45

Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
50 55 60

Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Thr Arg Lys
65 70 75 80

Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly Gln
85 90 95

```
Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr Lys
            100                 105                 110


<210> 356
<211> 102
<212> PRT
<213> Homo sapiens

<400> 356
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1               5                   10                  15


Leu Ala Val Ser Asp Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu
            20                  25                  30


Ala Gly Ile Val Met Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu
        35                  40                  45


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


Glu Ala Ala Thr Arg Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr
65                  70                  75                  80


Gln Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr
                85                  90                  95


Gln Arg Pro Tyr Tyr Lys
            100


<210> 357
<211> 101
<212> PRT
<213> Homo sapiens

<400> 357
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1               5                   10                  15


Leu Ala Val Ser Asp Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu
            20                  25                  30
```

```
Ala Gly Ile Val Met Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu
        35                  40                  45


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


Glu Ala Thr Arg Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln
65                  70                  75                  80


Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln
                85                  90                  95


Arg Pro Tyr Tyr Lys
            100


<210> 358
<211> 113
<212> PRT
<213> Homo sapiens

<400> 358
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1               5                   10                  15


Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
            20                  25                  30


Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
        35                  40                  45


Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
    50                  55                  60


Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Ala Thr Arg
65                  70                  75                  80


Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly
                85                  90                  95
```

Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr
100 105 110

Lys

<210> 359
<211> 112
<212> PRT
<213> Homo sapiens

<400> 359
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1 5 10 15

Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
20 25 30

Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
35 40 45

Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
50 55 60

Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Thr Arg Lys
65 70 75 80

Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly Gln
85 90 95

Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr Lys
100 105 110

<210> 360
<211> 102
<212> PRT
<213> Homo sapiens

<400> 360
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1 5 10 15

```
Leu Ala Val Ser Asp Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu
            20                  25                  30


Ala Gly Ile Val Met Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu
        35                  40                  45


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


Glu Ala Ala Thr Arg Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr
65                  70                  75                  80


Gln Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr
                85                  90                  95


Gln Arg Pro Tyr Tyr Lys
            100


<210> 361
<211> 101
<212> PRT
<213> Homo sapiens

<400> 361
Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1               5                   10                  15


Leu Ala Val Ser Asp Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu
            20                  25                  30


Ala Gly Ile Val Met Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu
        35                  40                  45


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


Glu Ala Thr Arg Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln
65                  70                  75                  80


Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln
                85                  90                  95
```

Arg Pro Tyr Tyr Lys
100

<210> 362
<211> 21
<212> PRT
<213> Homo sapiens

<400> 362
Glu Ser Pro Tyr Gln Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser
1 5 10 15

Asp Leu Asn Thr Gln
20

<210> 363
<211> 21
<212> PRT
<213> Homo sapiens

<400> 363
Glu Ser Pro Tyr Gln Glu Leu Gln Gly Gln Arg Ser Asp Val Tyr Ser
1 5 10 15

Asp Leu Asn Thr Gln
20

<210> 364
<211> 49
<212> PRT
<213> Homo sapiens

<400> 364
Arg Ser Gln Cys Met Trp Pro Arg Glu Thr Gln Leu Leu Leu Glu Val
1 5 10 15

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

Arg Gly Glu Arg Ser Ala Glu Glu Lys Gly Arg Leu Gly Asp Leu Trp
35 40 45

Val

<210> 365
<211> 35
<212> PRT
<213> Homo sapiens

<400> 365
Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn Gly Glu Phe
1 5 10 15

Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg Leu Thr Asp
20 25 30

Val Thr Leu
35

<210> 366
<211> 39
<212> PRT
<213> Homo sapiens

<400> 366
Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met
1 5 10 15

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

Glu Asn Cys Ser His His Leu
35

<210> 367
<211> 149
<212> PRT
<213> Homo sapiens

<400> 367
Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
1 5 10 15

Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
20 25 30

Thr Leu Ala Lys Ile Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
35 40 45

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
50 55 60

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
65 70 75 80

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
85 90 95

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
100 105 110

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
115 120 125

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
130 135 140

Ala Leu Pro Pro Arg
145

<210> 368
<211> 619
<212> PRT
<213> Homo sapiens

<400> 368
Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser
1 5 10 15

Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
20 25 30

Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
35 40 45

```
Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
    50                  55                  60

Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
65                  70                  75                  80

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

Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
            100                 105                 110

Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
        115                 120                 125

Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
    130                 135                 140

Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
145                 150                 155                 160

Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
                165                 170                 175

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

Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
        195                 200                 205

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

Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
225                 230                 235                 240

Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
                245                 250                 255
```

```
Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
            260                 265                 270

His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
        275                 280                 285

Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
    290                 295                 300

Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
305                 310                 315                 320

Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn
                325                 330                 335

Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val
            340                 345                 350

Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile
        355                 360                 365

Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met
    370                 375                 380

Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg
385                 390                 395                 400

Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met
                405                 410                 415

Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu
            420                 425                 430

Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly
        435                 440                 445

Met Lys Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala
    450                 455                 460
```

```
Arg Asn Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe
465                 470                 475                 480


Gly Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg
                485                 490                 495


Ser Ala Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn
            500                 505                 510


Phe Arg Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr
        515                 520                 525


Met Trp Glu Ala Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys
    530                 535                 540


Gly Pro Glu Val Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys
545                 550                 555                 560


Pro Pro Glu Cys Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp
                565                 570                 575


Ile Tyr Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg
            580                 585                 590


Met Arg Ala Cys Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro
        595                 600                 605


Gly Ser Thr Gln Lys Ala Glu Ala Ala Cys Ala
    610                 615


<210> 369
<211> 180
<212> PRT
<213> Homo sapiens

<400> 369
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15


Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30
```

```
Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
        35                  40                  45

Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
    50                  55                  60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65                  70                  75                  80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
                85                  90                  95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145                 150                 155                 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                165                 170                 175

Phe Trp Val Arg
            180
```

<210> 370
<211> 240
<212> PRT
<213> Homo sapiens

```
<400> 370
Met Gly Asn Ser Cys Tyr Asn Ile Val Ala Thr Leu Leu Leu Val Leu
1               5                   10                  15
```

```
Asn Phe Glu Arg Thr Arg Ser Leu Gln Asp Pro Cys Ser Asn Cys Pro
            20                  25                  30

Ala Gly Thr Phe Cys Asp Asn Asn Arg Asn Gln Ile Cys Ser Pro Cys
        35                  40                  45

Pro Pro Asn Ser Phe Ser Ser Ala Gly Gly Gln Arg Thr Cys Asp Ile
    50                  55                  60

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

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

Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu
            100                 105                 110

Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln
        115                 120                 125

Lys Arg Gly Ile Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Lys
    130                 135                 140

Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro
145                 150                 155                 160

Ser Pro Ala Asp Leu Ser Pro Gly Ala Ser Ser Val Thr Pro Pro Ala
                165                 170                 175

Pro Ala Arg Glu Pro Gly His Ser Pro Gln Ile Ile Ser Phe Phe Leu
            180                 185                 190

Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu
        195                 200                 205

Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
    210                 215                 220
```

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
225 230 235 240

<210> 371
<211> 86
<212> PRT
<213> Homo sapiens

<400> 371
Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Leu Val Glu Gln Ala
1 5 10 15

Ala Ala Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu
20 25 30

Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile
35 40 45

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

Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys
65 70 75 80

His Glu Lys Pro Pro Gln
85

<210> 372
<211> 21
<212> PRT
<213> Homo sapiens

<400> 372
Asp Gly Val Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu Thr Tyr Glu
1 5 10 15

Thr Leu Lys His Glu
20

<210> 373
<211> 66
<212> PRT
<213> Homo sapiens

<400> 373
Asp Pro Lys Leu Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu Tyr Gly
1   5   10   15

Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val Arg Lys
            20   25   30

Ala Ala Ile Thr Ser Tyr Glu Lys Ser Asp Gly Val Tyr Thr Gly Leu
        35   40   45

Ser Thr Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys His Glu Lys Pro
    50   55   60

Pro Gln
65

<210> 374
<211> 21
<212> PRT
<213> Homo sapiens

<400> 374
Asp Gly Val Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu Thr Tyr Glu
1   5   10   15

Thr Leu Lys His Glu
            20

<210> 375
<211> 46
<212> PRT
<213> Homo sapiens

<400> 375
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 Ile
        35   40   45

<210> 376
<211> 31
<212> PRT
<213> Homo sapiens

<400> 376
Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu
1 5 10 15

Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val Lys Arg Gly Arg
20 25 30

<210> 377
<211> 27
<212> PRT
<213> Homo sapiens

<400> 377
Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu
1 5 10 15

Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val
20 25

<210> 378
<211> 26
<212> PRT
<213> Homo sapiens

<400> 378
Val Ala Ala Ile Leu Gly Leu Gly Leu Val Leu Gly Leu Leu Gly Pro
1 5 10 15

Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu
20 25

<210> 379
<211> 363
<212> PRT
<213> Homo sapiens

<400> 379
Ala Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly
1 5 10 15

```
Gly Phe Ile Phe Trp Arg Lys Lys Arg Lys Asp Ala Lys Asn Asn Glu
            20                  25                  30

Val Ser Phe Ser Gln Ile Lys Pro Lys Lys Ser Lys Leu Ile Arg Val
        35                  40                  45

Glu Asn Phe Glu Ala Tyr Phe Lys Lys Gln Gln Ala Asp Ser Asn Cys
    50                  55                  60

Gly Phe Ala Glu Glu Tyr Glu Asp Leu Lys Leu Val Gly Ile Ser Gln
65                  70                  75                  80

Pro Lys Tyr Ala Ala Glu Leu Ala Glu Asn Arg Gly Lys Asn Arg Tyr
                85                  90                  95

Asn Asn Val Leu Pro Tyr Asp Ile Ser Arg Val Lys Leu Ser Val Gln
            100                 105                 110

Thr His Ser Thr Asp Asp Tyr Ile Asn Ala Asn Tyr Met Pro Gly Tyr
        115                 120                 125

His Ser Lys Lys Asp Phe Ile Ala Thr Gln Gly Pro Leu Pro Asn Thr
    130                 135                 140

Leu Lys Asp Phe Trp Arg Met Val Trp Glu Lys Asn Val Tyr Ala Ile
145                 150                 155                 160

Ile Met Leu Thr Lys Cys Val Glu Gln Gly Arg Thr Lys Cys Glu Glu
                165                 170                 175

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

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

Thr Val Lys Asn Ile Gln Thr Ser Glu Ser His Pro Leu Arg Gln Phe
    210                 215                 220
```

```
His Phe Thr Ser Trp Pro Asp His Gly Val Pro Asp Thr Thr Asp Leu
225                 230                 235                 240


Leu Ile Asn Phe Arg Tyr Leu Val Arg Asp Tyr Met Lys Gln Ser Pro
                245                 250                 255


Pro Glu Ser Pro Ile Leu Val His Cys Ser Ala Gly Val Gly Arg Thr
            260                 265                 270


Gly Thr Phe Ile Ala Ile Asp Arg Leu Ile Tyr Gln Ile Glu Asn Glu
        275                 280                 285


Asn Thr Val Asp Val Tyr Gly Ile Val Tyr Asp Leu Arg Met His Arg
    290                 295                 300


Pro Leu Met Val Gln Thr Glu Asp Gln Tyr Val Phe Leu Asn Gln Cys
305                 310                 315                 320


Val Leu Asp Ile Val Arg Ser Gln Lys Asp Ser Lys Val Asp Leu Ile
                325                 330                 335


Tyr Gln Asn Thr Thr Ala Met Thr Ile Tyr Glu Asn Leu Ala Pro Val
            340                 345                 350


Thr Thr Phe Gly Lys Thr Asn Gly Tyr Ile Ala
        355                 360


<210> 380
<211> 21
<212> PRT
<213> Homo sapiens

<400> 380
Ala Val Phe Gly Cys Ile Phe Gly Ala Leu Val Ile Val Thr Val Gly
1               5                   10                  15


Gly Phe Ile Phe Trp
            20
```

<210> 381
<211> 185
<212> PRT
<213> Homo sapiens

<400> 381

```
Lys Glu Ile Thr Asn Ala Leu Glu Thr Trp Gly Ala Leu Gly Gln Asp
1               5                  10                  15

Ile Asn Leu Asp Ile Pro Ser Phe Gln Met Ser Asp Asp Ile Asp Asp
            20                  25                  30

Ile Lys Trp Glu Lys Thr Ser Asp Lys Lys Lys Ile Ala Gln Phe Arg
        35                  40                  45

Lys Glu Lys Glu Thr Phe Lys Glu Lys Asp Thr Tyr Lys Leu Phe Lys
    50                  55                  60

Asn Gly Thr Leu Lys Ile Lys His Leu Lys Thr Asp Asp Gln Asp Ile
65                  70                  75                  80

Tyr Lys Val Ser Ile Tyr Asp Thr Lys Gly Lys Asn Val Leu Glu Lys
                85                  90                  95

Ile Phe Asp Leu Lys Ile Gln Glu Arg Val Ser Lys Pro Lys Ile Ser
            100                 105                 110

Trp Thr Cys Ile Asn Thr Thr Leu Thr Cys Glu Val Met Asn Gly Thr
        115                 120                 125

Asp Pro Glu Leu Asn Leu Tyr Gln Asp Gly Lys His Leu Lys Leu Ser
    130                 135                 140

Gln Arg Val Ile Thr His Lys Trp Thr Thr Ser Leu Ser Ala Lys Phe
145                 150                 155                 160

Lys Cys Thr Ala Gly Asn Lys Val Ser Lys Glu Ser Ser Val Glu Pro
                165                 170                 175

Val Ser Cys Pro Glu Lys Gly Leu Asp
            180                 185
```

<210> 382
<211> 106
<212> PRT
<213> Homo sapiens

<400> 382
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1   5   10   15

Gly Thr Ile Thr His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
            20   25   30

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

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala His Ile Phe Trp
    50   55   60

Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
65   70   75   80

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
                85   90   95

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            100   105

<210> 383
<211> 27
<212> PRT
<213> Homo sapiens

<400> 383
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1   5   10   15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
            20   25

<210> 384
<211> 66

<212> PRT
<213> Homo sapiens

<400> 384
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1   5   10   15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
            20   25   30

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

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
    50   55   60

Trp Val
65

<210> 385
<211> 33
<212> PRT
<213> Homo sapiens

<400> 385
Ile Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1   5   10   15

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
            20   25   30

Arg

<210> 386
<211> 68
<212> PRT
<213> Homo sapiens

<400> 386
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1   5   10   15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
20 25 30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
35 40 45

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
50 55 60

Ala Tyr Arg Ser
65

<210> 387
<211> 28
<212> PRT
<213> Homo sapiens

<400> 387
Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1 5 10 15

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> 388
<211> 26
<212> PRT
<213> Homo sapiens

<400> 388
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe His Phe Trp Val
20 25

<210> 389
<211> 28
<212> PRT
<213> Homo sapiens

<400> 389
Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1 5 10 15

Gly Gly Val Thr Val Ala Phe Ile Ile Phe Trp Val
            20   25

<210> 390
<211> 26
<212> PRT
<213> Homo sapiens

<400> 390
Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu
1   5   10   15

Val Thr Val Ala Phe Ile Ile Phe Trp Val
            20   25

<210> 391
<211> 69
<212> PRT
<213> Homo sapiens

<400> 391
Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1   5   10   15

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
            20   25   30

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
        35   40   45

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
    50   55   60

Ala Ala Tyr Arg Ser
65

<210> 392
<211> 180
<212> PRT
<213> Homo sapiens

<400> 392

```
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1               5                   10                  15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
            20                  25                  30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
        35                  40                  45

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
    50                  55                  60

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
65                  70                  75                  80

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
                85                  90                  95

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
            100                 105                 110

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
        115                 120                 125

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
    130                 135                 140

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
145                 150                 155                 160

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
                165                 170                 175

Leu Pro Pro Arg
            180
```

<210> 393
<211> 216
<212> PRT
<213> Homo sapiens

<400> 393
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1   5   10   15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
            20   25   30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
        35   40   45

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
    50   55   60

Ala Tyr Arg Ser Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro
65   70   75   80

Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp
                85   90   95

Ala His Ser Thr Leu Ala Lys Ile Arg Val Lys Phe Ser Arg Ser Ala
            100   105   110

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
        115   120   125

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
    130   135   140

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
145   150   155   160

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
                165   170   175

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
            180   185   190

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
        195   200   205

His Met Gln Ala Leu Pro Pro Arg
    210   215

<210> 394
<211> 140
<212> PRT
<213> Homo sapiens

<400> 394
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1   5   10   15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Arg Val Lys Phe
            20   25   30

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
        35   40   45

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
    50   55   60

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
65   70   75   80

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
                85   90   95

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
            100   105   110

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
        115   120   125

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    130   135   140

<210> 395
<211> 222
<212> PRT
<213> Homo sapiens

<400> 395
Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu
1   5   10   15

Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro
            20   25   30

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

Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe
    50   55   60

Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp
65   70   75   80

Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr
                85   90   95

Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val
            100   105   110

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
        115   120   125

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
    130   135   140

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
145   150   155   160

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
                165   170   175

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
            180   185   190

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
        195   200   205

```
Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    210                 215                 220


<210> 396
<211> 23
<212> PRT
<213> Homo sapiens

<400> 396
Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu
1               5                   10                  15


Thr Ala Leu Phe Leu Arg Val
            20


<210> 397
<211> 51
<212> PRT
<213> Homo sapiens

<400> 397
Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1               5                   10                  15


Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
            20                  25                  30


Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
        35                  40                  45


Leu Phe Leu
    50


<210> 398
<211> 21
<212> PRT
<213> Homo sapiens

<400> 398
Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu
1               5                   10                  15
```

Thr Ala Leu Phe Leu
            20

<210> 399
<211> 25
<212> PRT
<213> Homo sapiens

<400> 399
Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly
1   5   10   15

Leu Gly Ile Phe Phe Cys Val Arg Cys
            20   25

<210> 400
<211> 22
<212> PRT
<213> Homo sapiens

<400> 400
Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile
1   5   10   15

Gly Leu Gly Ile Phe Phe
            20

<210> 401
<211> 725
<212> PRT
<213> Homo sapiens

<400> 401
Ala Leu Ile Ala Phe Leu Ala Phe Leu Ile Ile Val Thr Ser Ile Ala
1   5   10   15

Leu Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser
            20   25   30

Cys Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys
        35   40   45

Gln Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr
    50   55   60

```
Tyr Lys Arg Lys Ile Ala Asp Glu Gly Arg Leu Phe Leu Ala Glu Phe
65                  70                  75                  80

Gln Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg
                85                  90                  95

Lys Pro Phe Asn Gln Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr
            100                 105                 110

Asp Tyr Asn Arg Val Glu Leu Ser Glu Ile Asn Gly Asp Ala Gly Ser
        115                 120                 125

Asn Tyr Ile Asn Ala Ser Tyr Ile Asp Gly Phe Lys Glu Pro Arg Lys
    130                 135                 140

Tyr Ile Ala Ala Gln Gly Pro Arg Asp Glu Thr Val Asp Asp Phe Trp
145                 150                 155                 160

Arg Met Ile Trp Glu Gln Lys Ala Thr Val Ile Val Met Val Thr Arg
                165                 170                 175

Cys Glu Glu Gly Asn Arg Asn Lys Cys Ala Glu Tyr Trp Pro Ser Met
            180                 185                 190

Glu Glu Gly Thr Arg Ala Phe Gly Asp Val Val Val Lys Ile Asn Gln
        195                 200                 205

His Lys Arg Cys Pro Asp Tyr Ile Ile Gln Lys Leu Asn Ile Val Asn
    210                 215                 220

Lys Lys Glu Lys Ala Thr Gly Arg Glu Val Thr His Ile Gln Phe Thr
225                 230                 235                 240

Ser Trp Pro Asp His Gly Val Pro Glu Asp Pro His Leu Leu Leu Lys
                245                 250                 255

Leu Arg Arg Arg Val Asn Ala Phe Ser Asn Phe Phe Ser Gly Pro Ile
            260                 265                 270
```

```
Trp His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Tyr Ile Gly Ile
        275                 280                 285

Asp Ala Met Leu Glu Gly Leu Glu Ala Glu Asn Lys Val Asp Val Tyr
    290                 295                 300

Gly Tyr Val Val Lys Leu Arg Arg Gln Arg Cys Leu Met Val Gln Val
305                 310                 315                 320

Glu Ala Gln Tyr Ile Leu Ile His Gln Ala Leu Val Glu Tyr Asn Gln
                325                 330                 335

Phe Gly Glu Thr Glu Val Asn Leu Ser Glu Leu His Pro Tyr Leu His
            340                 345                 350

Asn Met Lys Lys Arg Asp Pro Pro Ser Glu Pro Ser Pro Leu Glu Ala
        355                 360                 365

Glu Phe Gln Arg Leu Pro Ser Tyr Arg Ser Trp Arg Thr Gln His Ile
    370                 375                 380

Gly Asn Gln Glu Glu Asn Lys Ser Lys Asn Arg Asn Ser Asn Val Ile
385                 390                 395                 400

Pro Tyr Asp Tyr Asn Arg Val Pro Leu Lys His Glu Leu Glu Met Ser
                405                 410                 415

Lys Glu Ser Glu His Asp Ser Asp Glu Ser Ser Asp Asp Asp Ser Asp
            420                 425                 430

Ser Glu Glu Pro Ser Lys Tyr Ile Asn Ala Ser Phe Ile Met Ser Tyr
        435                 440                 445

Trp Lys Pro Glu Val Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr
    450                 455                 460

Ile Gly Asp Phe Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile
465                 470                 475                 480
```

```
Val Met Leu Thr Glu Leu Lys His Gly Asp Gln Glu Ile Cys Ala Gln
                485                 490                 495

Tyr Trp Gly Glu Gly Lys Gln Thr Tyr Gly Asp Ile Glu Val Asp Leu
            500                 505                 510

Lys Asp Thr Asp Lys Ser Ser Thr Tyr Thr Leu Arg Val Phe Glu Leu
        515                 520                 525

Arg His Ser Lys Arg Lys Asp Ser Arg Thr Val Tyr Gln Tyr Gln Tyr
    530                 535                 540

Thr Asn Trp Ser Val Glu Gln Leu Pro Ala Glu Pro Lys Glu Leu Ile
545                 550                 555                 560

Ser Met Ile Gln Trp Lys Gln Lys Leu Pro Gln Lys Asn Ser Ser Glu
                565                 570                 575

Gly Asn Lys His His Lys Ser Thr Pro Leu Leu Ile His Cys Arg Asp
            580                 585                 590

Gly Ser Gln Gln Thr Gly Ile Phe Cys Ala Leu Leu Asn Leu Leu Glu
        595                 600                 605

Ser Ala Glu Thr Glu Glu Trp Asp Ile Phe Gln Trp Lys Ala Leu Arg
    610                 615                 620

Lys Ala Arg Pro Gly Met Val Ser Thr Phe Glu Gln Tyr Gln Phe Leu
625                 630                 635                 640

Tyr Asp Val Ile Ala Ser Thr Tyr Pro Ala Gln Asn Gly Gln Val Lys
                645                 650                 655

Lys Asn Asn His Gln Glu Asp Lys Ile Glu Phe Asp Asn Glu Val Asp
            660                 665                 670

Lys Val Lys Gln Asp Ala Asn Cys Val Asn Pro Leu Gly Ala Pro Glu
        675                 680                 685
```

```
Lys Leu Pro Glu Ala Lys Glu Gln Ala Glu Gly Ser Glu Pro Thr Ser
    690                 695                 700


Gly Thr Glu Gly Pro Glu His Ser Val Asn Gly Pro Ala Ser Pro Ala
705                 710                 715                 720


Leu Asn Gln Gly Ser
                725


<210> 402
<211> 23
<212> PRT
<213> Homo sapiens

<400> 402
Pro Leu Phe Ile Pro Val Ala Val Met Val Thr Ala Phe Ser Gly Leu
1               5                   10                  15


Ala Phe Ile Ile Trp Leu Ala
            20


<210> 403
<211> 24
<212> PRT
<213> Homo sapiens

<400> 403
Ala Leu Pro Ala Ala Leu Ala Val Ile Ser Phe Leu Leu Gly Leu Gly
1               5                   10                  15


Leu Gly Val Ala Cys Val Leu Ala
            20


<210> 404
<211> 21
<212> PRT
<213> Homo sapiens

<400> 404
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> 405
<211> 286
<212> PRT
<213> Homo sapiens

<400> 405
Ala Ala Ala Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr
1   5   10   15

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
            20   25   30

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
        35   40   45

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
    50   55   60

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
65   70   75   80

Tyr Cys Asn His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser
                85   90   95

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
            100   105   110

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg
        115   120   125

Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
    130   135   140

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
145   150   155   160

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
                165   170   175

```
Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
            180                 185                 190

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
        195                 200                 205

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
    210                 215                 220

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
225                 230                 235                 240

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
                245                 250                 255

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
            260                 265                 270

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
        275                 280                 285


<210> 406
<211> 226
<212> PRT
<213> Homo sapiens

<400> 406
Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
1               5                   10                  15

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
            20                  25                  30

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

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
    50                  55                  60
```

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
65 70 75 80

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
85 90 95

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
100 105 110

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
115 120 125

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
130 135 140

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
145 150 155 160

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
165 170 175

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
180 185 190

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
195 200 205

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
210 215 220

Pro Arg
225

<210> 407
<211> 83
<212> PRT
<213> Homo sapiens

<400> 407
Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
1 5 10 15

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            20   25   30

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        35   40   45

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    50   55   60

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
65   70   75   80

His Arg Asn

<210> 408
<211> 22
<212> PRT
<213> Homo sapiens

<400> 408
Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
1   5   10   15

Val Ile Thr Leu Tyr Cys
            20

<210> 409
<211> 24
<212> PRT
<213> Homo sapiens

<400> 409
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> 410
<211> 25

<212> PRT
<213> Homo sapiens

<400> 410
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 Arg
            20   25

<210> 411
<211> 71
<212> PRT
<213> Homo sapiens

<400> 411
Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
1   5   10   15

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

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

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
    50   55   60

Val Ile Thr Leu Tyr Cys Asn
65   70

<210> 412
<211> 25
<212> PRT
<213> Homo sapiens

<400> 412
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 Val Cys Arg
            20   25

<210> 413
<211> 21
<212> PRT
<213> Homo sapiens

<400> 413
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
20

<210> 414
<211> 23
<212> PRT
<213> Homo sapiens

<400> 414
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
20

<210> 415
<211> 101
<212> PRT
<213> Homo sapiens

<400> 415
Ala Pro Val Gly Leu Val Ala Arg Leu Ala Asp Glu Ser Gly His Val
1 5 10 15

Val Leu Arg Trp Leu Pro Pro Pro Glu Thr Pro Met Thr Ser His Ile
20 25 30

Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Gly Ala Gly Ser Val Gln
35 40 45

Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn Leu
50 55 60

Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala Glu
65 70 75 80

```
Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro Val Ser Leu
                85                  90                  95


Leu Thr Pro Ser Asp
            100


<210> 416
<211> 52
<212> PRT
<213> Homo sapiens

<400> 416
Phe Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly
1               5                   10                  15


Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys
            20                  25                  30


Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn
        35                  40                  45


Pro Lys Asn Asn
    50


<210> 417
<211> 257
<212> PRT
<213> Homo sapiens

<400> 417
Met Ala Pro Ala Met Glu Ser Pro Thr Leu Leu Cys Val Ala Leu Leu
1               5                   10                  15


Phe Phe Ala Pro Asp Gly Val Leu Ala Val Pro Gln Lys Pro Lys Val
            20                  25                  30


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


Leu Thr Cys Asn Gly Asn Asn Phe Phe Glu Val Ser Ser Thr Lys Trp
    50                  55                  60
```

```
Phe His Asn Gly Ser Leu Ser Glu Glu Thr Asn Ser Ser Leu Asn Ile
65                  70                  75                  80

Val Asn Ala Lys Phe Glu Asp Ser Gly Glu Tyr Lys Cys Gln His Gln
                85                  90                  95

Gln Val Asn Glu Ser Glu Pro Val Tyr Leu Glu Val Phe Ser Asp Trp
            100                 105                 110

Leu Leu Leu Gln Ala Ser Ala Glu Val Val Met Glu Gly Gln Pro Leu
        115                 120                 125

Phe Leu Arg Cys His Gly Trp Arg Asn Trp Asp Val Tyr Lys Val Ile
    130                 135                 140

Tyr Tyr Lys Asp Gly Glu Ala Leu Lys Tyr Trp Tyr Glu Asn His Asn
145                 150                 155                 160

Ile Ser Ile Thr Asn Ala Thr Val Glu Asp Ser Gly Thr Tyr Tyr Cys
                165                 170                 175

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

Thr Val Ile Lys Ala Pro Arg Glu Lys Tyr Trp Leu Gln Phe Phe Ile
        195                 200                 205

Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly Leu Phe Ile
    210                 215                 220

Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys Arg Thr Arg
225                 230                 235                 240

Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn Pro Lys Asn
                245                 250                 255

Asn
```

<210> 418
<211> 244
<212> PRT
<213> Homo sapiens

<400> 418
Met Asp Thr Glu Ser Asn Arg Arg Ala Asn Leu Ala Leu Pro Gln Glu
1   5   10   15

Pro Ser Ser Val Pro Ala Phe Glu Val Leu Glu Ile Ser Pro Gln Glu
            20   25   30

Val Ser Ser Gly Arg Leu Leu Lys Ser Ala Ser Ser Pro Pro Leu His
        35   40   45

Thr Trp Leu Thr Val Leu Lys Lys Glu Gln Glu Phe Leu Gly Val Thr
    50   55   60

Gln Ile Leu Thr Ala Met Ile Cys Leu Cys Phe Gly Thr Val Val Cys
65   70   75   80

Ser Val Leu Asp Ile Ser His Ile Glu Gly Asp Ile Phe Ser Ser Phe
                85   90   95

Lys Ala Gly Tyr Pro Phe Trp Gly Ala Ile Phe Phe Ser Ile Ser Gly
            100   105   110

Met Leu Ser Ile Ile Ser Glu Arg Arg Asn Ala Thr Tyr Leu Val Arg
        115   120   125

Gly Ser Leu Gly Ala Asn Thr Ala Ser Ser Ile Ala Gly Gly Thr Gly
    130   135   140

Ile Thr Ile Leu Ile Ile Asn Leu Lys Lys Ser Leu Ala Tyr Ile His
145   150   155   160

Ile His Ser Cys Gln Lys Phe Phe Glu Thr Lys Cys Phe Met Ala Ser
                165   170   175

```
Phe Ser Thr Glu Ile Val Val Met Met Leu Phe Leu Thr Ile Leu Gly
            180                 185                 190


Leu Gly Ser Ala Val Ser Leu Thr Ile Cys Gly Ala Gly Glu Glu Leu
        195                 200                 205


Lys Gly Asn Lys Val Pro Glu Asp Arg Val Tyr Glu Glu Leu Asn Ile
    210                 215                 220


Tyr Ser Ala Thr Tyr Ser Glu Leu Glu Asp Pro Gly Glu Met Ser Pro
225                 230                 235                 240


Pro Ile Asp Leu



<210> 419
<211> 86
<212> PRT
<213> Homo sapiens

<400> 419
Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Leu Val Glu Gln Ala
1               5                   10                  15


Ala Ala Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu
            20                  25                  30


Phe Leu Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile
        35                  40                  45


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


Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys
65                  70                  75                  80


His Glu Lys Pro Pro Gln
                85


<210> 420
<211> 54
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<212> PRT
<213> Homo sapiens

<400> 420
Asp Ile Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr
1   5   10   15

Gly Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile
            20   25   30

Lys Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro
        35   40   45

Asn Pro Lys Asn Asn Arg
    50

<210> 421
<211> 31
<212> PRT
<213> Homo sapiens

<400> 421
Pro Leu Gly Trp Leu Thr Val Val Leu Leu Ala Val Ala Ala Cys Val
1   5   10   15

Leu Leu Leu Thr Ser Ala Gln Leu Gly Leu His Ile Trp Gln Leu
            20   25   30

<210> 422
<211> 24
<212> PRT
<213> Homo sapiens

<400> 422
Ser Ile Ile Ser Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly
1   5   10   15

Val Val Phe Gly Ile Leu Ile Ile
            20

<210> 423
<211> 113
<212> PRT
<213> Homo sapiens

<400> 423
Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys Phe Gly
1   5   10   15

Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp Pro Pro
            20   25   30

Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr
        35   40   45

Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys
    50   55   60

Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys Gly Cys
65   70   75   80

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

Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly Ile Leu
            100   105   110

Ile

<210> 424
<211> 21
<212> PRT
<213> Homo sapiens

<400> 424
Phe Leu Val Ile Ile Val Ile Leu Ser Ala Leu Phe Leu Gly Thr Leu
1   5   10   15

Ala Cys Phe Cys Val
            20

<210> 425
<211> 68
<212> PRT
<213> Homo sapiens

<400> 425
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1   5   10   15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
            20   25   30

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
        35   40   45

Pro Thr Arg Lys His Tyr Gln Ala Tyr Ala Ala Ala Arg Asp Phe Ala
    50   55   60

Ala Tyr Arg Ser
65

<210> 426
<211> 5
<212> PRT
<213> Homo sapiens

<400> 426
Asp Lys Thr His Thr
1   5

<210> 427
<211> 4
<212> PRT
<213> Homo sapiens

<400> 427
Cys Pro Pro Cys
1

<210> 428
<211> 15
<212> PRT
<213> Homo sapiens

<400> 428
Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
1   5   10   15

<210> 429
<211> 12
<212> PRT
<213> Homo sapiens

<400> 429
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr
1 5 10

<210> 430
<211> 10
<212> PRT
<213> Homo sapiens

<400> 430
Lys Ser Cys Asp Lys Thr His Thr Cys Pro
1 5 10

<210> 431
<211> 7
<212> PRT
<213> Homo sapiens

<400> 431
Lys Cys Cys Val Asp Cys Pro
1 5

<210> 432
<211> 7
<212> PRT
<213> Homo sapiens

<400> 432
Lys Tyr Gly Pro Pro Cys Pro
1 5

<210> 433
<211> 16
<212> PRT
<213> Homo sapiens

<400> 433
Val Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 434
<211> 16

<212> PRT
<213> Homo sapiens

<400> 434
Leu Asp Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1   5   10   15

<210> 435
<211> 39
<212> PRT
<213> Homo sapiens

<400> 435
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1   5   10   15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
            20   25   30

Phe Pro Gly Pro Ser Lys Pro
        35

<210> 436
<211> 12
<212> PRT
<213> Homo sapiens

<400> 436
Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
1   5   10

<210> 437
<211> 45
<212> PRT
<213> Homo sapiens

<400> 437
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> 438
<211> 48
<212> PRT
<213> Homo sapiens

<400> 438
Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
1   5   10   15

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
            20   25   30

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

<210> 439
<211> 45
<212> PRT
<213> Homo sapiens

<400> 439
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> 440
<211> 45
<212> PRT
<213> Homo sapiens

<400> 440
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> 441
<211> 79
<212> PRT
<213> Homo sapiens

<400> 441
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 Glu Pro Lys
35 40 45

Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val
50 55 60

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
65 70 75

<210> 442
<211> 51
<212> PRT
<213> Homo sapiens

<400> 442
Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
1 5 10 15

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
20 25 30

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

Asp Ile Tyr
50

<210> 443
<211> 69
<212> PRT
<213> Homo sapiens

<400> 443
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 Ile Tyr Ile
35 40 45

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
50 55 60

Ile Thr Leu Tyr Cys
65

<210> 444
<211> 44
<212> PRT
<213> Homo sapiens

<400> 444
Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
1 5 10 15

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

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

<210> 445
<211> 47
<212> PRT
<213> Homo sapiens

<400> 445
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 Ile Tyr
        35   40   45

<210> 446
<211> 11
<212> PRT
<213> Homo sapiens

<400> 446
Leu Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1   5   10

<210> 447
<211> 101
<212> PRT
<213> Homo sapiens

<400> 447
Ala Pro Val Gly Leu Val Ala Arg Leu Ala Asp Glu Ser Gly His Val
1   5   10   15

Val Leu Arg Trp Leu Pro Pro Pro Glu Thr Pro Met Thr Ser His Ile
            20   25   30

Arg Tyr Glu Val Asp Val Ser Ala Gly Asn Gly Ala Gly Ser Val Gln
        35   40   45

Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn Leu
    50   55   60

Arg Gly Arg Thr Arg Tyr Thr Phe Ala Val Arg Ala Arg Met Ala Glu
65   70   75   80

Pro Ser Phe Gly Gly Phe Trp Ser Ala Trp Ser Glu Pro Val Ser Leu
                85   90   95

Leu Thr Pro Ser Asp
            100

<210> 448
<211> 16
<212> PRT
<213> Homo sapiens

<400> 448
Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
1   5   10   15

<210> 449
<211> 16
<212> PRT
<213> Homo sapiens

<400> 449
Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
1   5   10   15

<210> 450
<211> 282
<212> PRT
<213> Homo sapiens

<400> 450
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1   5   10   15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20   25   30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35   40   45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50   55   60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65   70   75   80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85   90   95

```
Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280
```

<210> 451
<211> 246
<212> PRT
<213> Homo sapiens

<400> 451
Tyr Val Thr Val Ser Ser Gln Asp Pro Ala Glu Pro Lys Ser Pro Asp
1   5   10   15

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            20   25   30

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        35   40   45

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    50   55   60

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
65   70   75   80

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                85   90   95

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            100   105   110

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        115   120   125

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    130   135   140

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
145   150   155   160

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                165   170   175

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            180   185   190

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        195   200   205

```
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    210                 215                 220


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
225                 230                 235                 240


Gly Lys Lys Asp Pro Lys
                245


<210> 452
<211> 45
<212> PRT
<213> Homo sapiens

<400> 452
Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
1               5                   10                  15


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


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


<210> 453
<211> 16
<212> PRT
<213> Homo sapiens

<400> 453
Leu Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1               5                   10                  15


<210> 454
<211> 43
<212> PRT
<213> Homo sapiens

<400> 454
Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
1               5                   10                  15
```

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

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
35 40

<210> 455
<211> 15
<212> PRT
<213> Homo sapiens

<400> 455
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 456
<211> 16
<212> PRT
<213> Homo sapiens

<400> 456
Glu Leu Lys Thr Pro Leu Gly Asp Thr His Thr Cys Pro Arg Cys Pro
1 5 10 15

<210> 457
<211> 15
<212> PRT
<213> Homo sapiens

<400> 457
Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
1 5 10 15

<210> 458
<211> 12
<212> PRT
<213> Homo sapiens

<400> 458
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 459
<211> 12
<212> PRT
<213> Homo sapiens

<400> 459
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1   5   10

<210> 460
<211> 229
<212> PRT
<213> Homo sapiens

<400> 460
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1   5   10   15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20   25   30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35   40   45

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65   70   75   80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85   90   95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100   105   110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115   120   125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130   135   140

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

```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190


Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220


Leu Ser Leu Gly Lys
225


<210> 461
<211> 119
<212> PRT
<213> Homo sapiens

<400> 461
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gln Pro Arg
1               5                   10                  15


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
            20                  25                  30


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
        35                  40                  45


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    50                  55                  60


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
65                  70                  75                  80


Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
                85                  90                  95


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            100                 105                 110
```

Leu Ser Leu Ser Leu Gly Lys
        115

<210> 462
<211> 282
<212> PRT
<213> Homo sapiens

<400> 462
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1   5   10   15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20   25   30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35   40   45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50   55   60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65   70   75   80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85   90   95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100   105   110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115   120   125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130   135   140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145   150   155   160

```
Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280
```

<210> 463
<211> 281
<212> PRT
<213> Homo sapiens

<400> 463

```
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1               5                   10                  15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20                  25                  30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60
```

```
Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu His Pro Ser Leu Pro Pro Gln
145                 150                 155                 160

Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys Leu
                165                 170                 175

Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser Trp
            180                 185                 190

Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu Met
        195                 200                 205

Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro Ala
    210                 215                 220

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

Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr Cys
                245                 250                 255

Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg Ser
            260                 265                 270
```

Leu Glu Val Ser Tyr Val Thr Asp His
        275   280

<210> 464
<211> 283
<212> PRT
<213> Homo sapiens

<400> 464
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1   5   10   15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20   25   30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35   40   45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50   55   60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65   70   75   80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85   90   95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100   105   110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115   120   125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130   135   140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145   150   155   160

```
Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Val Val Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala
    210                 215                 220

Pro Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp
225                 230                 235                 240

Ser Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr
                245                 250                 255

Thr Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser
            260                 265                 270

Arg Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280


<210> 465
<211> 58
<212> PRT
<213> Homo sapiens

<400> 465
Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln
1               5                   10                  15

Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg
            20                  25                  30

Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys Glu Lys Glu
        35                  40                  45

Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro
    50                  55
```

<210> 466
<211> 282
<212> PRT
<213> Homo sapiens

<400> 466
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1   5   10   15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20   25   30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35   40   45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50   55   60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65   70   75   80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85   90   95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100   105   110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115   120   125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130   135   140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145   150   155   160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165   170   175

```
Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190


Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205


Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220


Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240


Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255


Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270


Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280


<210> 467
<211> 282
<212> PRT
<213> Homo sapiens

<400> 467
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1               5                   10                  15


Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20                  25                  30


Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45


Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60


Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80
```

```
Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280
```

<210> 468
<211> 282
<212> PRT
<213> Homo sapiens

<400> 468
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1   5   10   15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20   25   30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35   40   45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50   55   60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65   70   75   80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85   90   95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100   105   110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115   120   125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130   135   140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145   150   155   160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165   170   175

```
Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190


Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205


Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220


Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240


Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255


Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270


Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280


<210> 469
<211> 282
<212> PRT
<213> Homo sapiens

<400> 469
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1               5                   10                  15


Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20                  25                  30


Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45


Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60


Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80
```

```
Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280
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<210> 470
<211> 234
<212> PRT
<213> Homo sapiens

<220>
<221> MOD_RES
<222> (91)..(91)
<223> Selenocysteine

<400> 470
Ala Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Xaa Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

```
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175


Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220


Ser Leu Ser Leu Ser Pro Gly Lys Lys Asp
225                 230


<210> 471
<211> 234
<212> PRT
<213> Homo sapiens

<400> 471
Ala Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1               5                   10                  15


Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30


Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45


Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60


Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80


Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95
```

```
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110


Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125


Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130                 135                 140


Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160


Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175


Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220


Ser Leu Ser Leu Ser Pro Gly Lys Lys Asp
225                 230


<210> 472
<211> 20
<212> PRT
<213> Homo sapiens

<400> 472
Ala Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1               5                   10                  15


Lys Asp Pro Lys
            20


<210> 473
<211> 15
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<212> PRT
<213> Homo sapiens

<400> 473
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 474
<211> 233
<212> PRT
<213> Homo sapiens

<400> 474
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Val Lys Cys Lys Val Ser Asn Lys Ala Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

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


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
            180                 185                 190


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220


Leu Ser Leu Ser Pro Gly Lys Lys Asp
225                 230


<210> 475
<211> 13
<212> PRT
<213> Homo sapiens

<400> 475
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                   10


<210> 476
<211> 231
<212> PRT
<213> Homo sapiens

<400> 476
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15


Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30


Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45


Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

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

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 477
<211> 235
<212> PRT
<213> Homo sapiens

<400> 477

```
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                  10                  15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

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

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205
```

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys
225 230 235

<210> 478
<211> 223
<212> PRT
<213> Homo sapiens

<400> 478
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1 5 10 15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
20 25 30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
50 55 60

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
65 70 75 80

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
85 90 95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
100 105 110

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
115 120 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
130 135 140

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
145 150 155 160

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
165 170 175

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
195 200 205

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215 220

<210> 479
<211> 235
<212> PRT
<213> Homo sapiens

<400> 479
Asp Pro Ala Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        115                 120                 125


Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
    130                 135                 140


Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145                 150                 155                 160


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


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            180                 185                 190


Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
        195                 200                 205


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
    210                 215                 220


Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys
225                 230                 235


<210> 480
<211> 12
<212> PRT
<213> Homo sapiens

<400> 480
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1               5                   10


<210> 481
<211> 17
<212> PRT
<213> Homo sapiens

<400> 481
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys
1               5                   10                  15
```

Pro

<210> 482
<211> 61
<212> PRT
<213> Homo sapiens

<400> 482
Glu Leu Lys Thr Pro Leu Gly Asp Thr His Thr Cys Pro Arg Cys Pro
1 5 10 15

Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu
20 25 30

Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro
35 40 45

Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
50 55 60

<210> 483
<211> 230
<212> PRT
<213> Homo sapiens

<400> 483
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

```
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys Met
225                 230
```

<210> 484
<211> 230
<212> PRT
<213> Homo sapiens

<400> 484

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30
```

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys Met
225                 230
```

<210> 485
<211> 12
<212> PRT
<213> Homo sapiens

<400> 485
Ser Pro Asn Met Val Pro His Ala His His Ala Gln
1   5   10

<210> 486
<211> 107
<212> PRT
<213> Homo sapiens

<400> 486
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
1   5   10   15

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            20   25   30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35   40   45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50   55   60

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
65   70   75   80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85   90   95

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
            100   105

<210> 487
<211> 129
<212> PRT
<213> Homo sapiens

<400> 487

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
20 25 30

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
35 40 45

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
50 55 60

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

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
85 90 95

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
100 105 110

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
115 120 125

Lys

<210> 488
<211> 229
<212> PRT
<213> Homo sapiens

<400> 488
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

```
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Gln Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Val Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225
```

<210> 489
<211> 229

<212> PRT
<213> Homo sapiens

<400> 489

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                  10                  15

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

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

Glu Val His Gln Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Val Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190
```

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Lys
225

<210> 490
<211> 230
<212> PRT
<213> Homo sapiens

<400> 490
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

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

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
165 170 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Lys Met
225 230

<210> 491
<211> 36
<212> DNA
<213> Homo sapiens

<400> 491
gaatctaagt acggaccgcc ctgccccct tgccct 36

<210> 492
<211> 12
<212> PRT
<213> Homo sapiens

<400> 492
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 493
<211> 119
<212> PRT
<213> Homo sapiens

<400> 493
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gln Pro Arg

1 5 10 15

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
20 25 30

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
35 40 45

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
50 55 60

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
65 70 75 80

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
85 90 95

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
100 105 110

Leu Ser Leu Ser Leu Gly Lys
115

<210> 494
<211> 229
<212> PRT
<213> Homo sapiens

<400> 494
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

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

```
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225


<210> 495
<211> 229
<212> PRT
<213> Homo sapiens

<400> 495
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
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```
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
```

210 215 220

Leu Ser Leu Gly Lys
225

<210> 496
<211> 12
<212> PRT
<213> Homo sapiens

<400> 496
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 497
<211> 9
<212> PRT
<213> Homo sapiens

<400> 497
Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5

<210> 498
<211> 10
<212> PRT
<213> Homo sapiens

<400> 498
Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 499
<211> 13
<212> PRT
<213> Homo sapiens

<400> 499
Glu Val Val Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 500
<211> 229
<212> PRT
<213> Homo sapiens

<400> 500

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1               5                  10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Leu Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205
```

```
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220


Leu Ser Leu Gly Lys
225


<210> 501
<211> 22
<212> PRT
<213> Homo sapiens

<400> 501
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1               5                   10                  15


Ser Gly Gly Gly Ser Gly
            20


<210> 502
<211> 231
<212> PRT
<213> Homo sapiens

<400> 502
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15


Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30


Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45


Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95
```

```
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110


Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175


Thr Ile Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220


Leu Ser Leu Ser Pro Gly Lys
225                 230


<210> 503
<211> 231
<212> PRT
<213> Homo sapiens

<400> 503
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15


Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30


Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
```

```
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Leu Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Ile Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 504

<211> 231
<212> PRT
<213> Homo sapiens

<400> 504
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20   25   30

Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
        35   40   45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50   55   60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65   70   75   80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85   90   95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100   105   110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115   120   125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130   135   140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145   150   155   160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165   170   175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180   185   190

```
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220


Leu Ser Leu Ser Pro Gly Lys
225                 230


<210> 505
<211> 68
<212> PRT
<213> Homo sapiens

<400> 505
Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
1               5                   10                  15


Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
            20                  25                  30


Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
        35                  40                  45


Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
    50                  55                  60


Thr Leu Tyr Cys
65


<210> 506
<211> 243
<212> PRT
<213> Homo sapiens

<400> 506
Asp Ile Gln Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly
1               5                   10                  15


Gly Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
            20                  25                  30
```

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
        35                  40                  45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Phe
                85                  90                  95

Thr Phe Gly Ser 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 Gln Val Gln Leu Lys Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Ser
    130                 135                 140

Thr Val Ser Gly Phe Ser Leu Ser Arg Tyr Ser Val His Trp Val Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu Gly Met Ile Trp Gly Gly
                165                 170                 175

Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln
        195                 200                 205

Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala Arg Asn Glu Gly Asp Thr
    210                 215                 220

Thr Ala Gly Thr Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240
```

Val Ser Ser

<210> 507
<211> 62
<212> PRT
<213> Homo sapiens

<400> 507
Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe Val Pro Val Phe
1 5 10 15

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            20 25 30

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        35 40 45

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    50 55 60

<210> 508
<211> 68
<212> PRT
<213> Homo sapiens

<400> 508
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 Ile Tyr Ile
        35 40 45

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
    50 55 60

Ile Thr Leu Tyr
65

<210> 509
<211> 70
<212> PRT
<213> Homo sapiens

<400> 509
Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
1 5 10 15

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
            20 25 30

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
        35 40 45

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
    50 55 60

Leu Val Ile Thr Leu Tyr
65 70

<210> 510
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 510
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50 55 60

```
Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270
```

```
Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser
        275                 280                 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
    290                 295                 300

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
305                 310                 315                 320

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                325                 330                 335

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
            340                 345                 350

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
        355                 360                 365

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
    370                 375                 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385                 390                 395                 400

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
                405                 410                 415

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            420                 425                 430

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
        435                 440                 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
    450                 455                 460

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480
```

```
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
                485                 490                 495

Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
            500                 505                 510

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
        515                 520                 525

Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
    530                 535                 540

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
545                 550                 555                 560

Ala Ala Tyr Arg Ser Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala
                565                 570                 575

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
            580                 585                 590

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
        595                 600                 605

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
    610                 615                 620

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
625                 630                 635                 640

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
                645                 650                 655

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
            660                 665                 670

His Met Gln Ala Leu Pro Pro Arg
        675                 680
```

<210> 511
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 511

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15


Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20                  25                  30


Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45


Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60


Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95


Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110


Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125


Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140


Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160


Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
```

```
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
        275                 280                 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
    290                 295                 300

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
305                 310                 315                 320

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                325                 330                 335

Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val
            340                 345                 350

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
        355                 360                 365

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
```

```
    370                 375                 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385                 390                 395                 400

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
                405                 410                 415

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            420                 425                 430

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
        435                 440                 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
    450                 455                 460

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
                485                 490                 495

Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
            500                 505                 510

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
        515                 520                 525

Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
    530                 535                 540

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
545                 550                 555                 560

Ala Ala Tyr Arg Ser Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala
                565                 570                 575

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
```

580 585 590

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
595 600 605

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
610 615 620

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
625 630 635 640

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
645 650 655

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
660 665 670

His Met Gln Ala Leu Pro Pro Arg
675 680

<210> 512
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 512
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
50 55 60

```
Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270
```

```
Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser
        275                 280                 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
    290                 295                 300

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
305                 310                 315                 320

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                325                 330                 335

Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val
            340                 345                 350

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
        355                 360                 365

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
    370                 375                 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385                 390                 395                 400

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
                405                 410                 415

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            420                 425                 430

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
        435                 440                 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
    450                 455                 460

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480
```

```
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
                485                 490                 495

Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
            500                 505                 510

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
        515                 520                 525

Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
    530                 535                 540

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
545                 550                 555                 560

Ala Ala Tyr Arg Ser Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala
                565                 570                 575

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
            580                 585                 590

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
        595                 600                 605

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
    610                 615                 620

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
625                 630                 635                 640

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
                645                 650                 655

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
            660                 665                 670

His Met Gln Ala Leu Pro Pro Arg
        675                 680
```

<210> 513
<211> 580
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 513
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
50 55 60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
100 105 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
115 120 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
130 135 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145 150 155 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu

```
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270

Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser Ser Gly Gly Gly Ser
        275                 280                 285

Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
    290                 295                 300

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
305                 310                 315                 320

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
                325                 330                 335

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
            340                 345                 350

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
        355                 360                 365

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
```

```
    370                 375                 380

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Phe Trp Val
385                 390                 395                 400

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
                405                 410                 415

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Gly Gly
            420                 425                 430

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
        435                 440                 445

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
    450                 455                 460

Ser Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
465                 470                 475                 480

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
                485                 490                 495

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
            500                 505                 510

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
        515                 520                 525

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
    530                 535                 540

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
545                 550                 555                 560

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
                565                 570                 575

Leu Pro Pro Arg
```

580

<210> 514
<211> 711
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 514

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Leu Cys Glu Leu Pro His
1 5 10 15

Pro Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Gln Thr Thr
20 25 30

Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg
35 40 45

Ala Ser Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys
50 55 60

Pro Asp Gly Thr Val Lys Leu Leu Leu Ile Tyr His Thr Ser Arg Leu
65 70 75 80

His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Gly Ser Gly Thr
85 90 95

Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr
100 105 110

Tyr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly
115 120 125

Gly Thr Lys Leu Glu Ile Ile Thr Gly Ser Thr Ser Gly Ser Gly Lys
130 135 140

Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Glu Val Lys Leu Gln
145 150 155 160

```
Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr
                165                 170                 175

Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp
            180                 185                 190

Ile Arg Gln Pro Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
        195                 200                 205

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Ala Leu Lys Ser Arg
    210                 215                 220

Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Lys
225                 230                 235                 240

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
                245                 250                 255

His Tyr Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            260                 265                 270

Gly Thr Ser Val Thr Val Ser Ser Glu Glu Ser Lys Tyr Gly Pro Pro
        275                 280                 285

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Ser Val
    290                 295                 300

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
305                 310                 315                 320

Pro Glu Val Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
                325                 330                 335

Glu Val Gln Phe Asn Trp Tyr Val Val Asp Gly Val Glu Val His Asn
            340                 345                 350

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Thr Tyr Arg
        355                 360                 365
```

```
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
    370                 375                 380

Glu Tyr Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
385                 390                 395                 400

Glu Lys Thr Ile Ser Lys Ala Ala Lys Gly Gln Pro Arg Glu Pro Gln
                405                 410                 415

Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Thr Lys Asn Gln
            420                 425                 430

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        435                 440                 445

Val Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    450                 455                 460

Thr Pro Pro Val Leu Asp Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
465                 470                 475                 480

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Glu Gly Asn Val Phe
                485                 490                 495

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
            500                 505                 510

Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Phe Trp Val Leu Val Val
        515                 520                 525

Val Gly Gly Val Leu Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
    530                 535                 540

Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Arg Ser Arg Gly Gly His
545                 550                 555                 560

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Arg
                565                 570                 575
```

```
Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
            580                 585                 590


Ser Arg Val Lys Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
        595                 600                 605


Gln Gly Gln Asn Gln Leu Tyr Asn Glu Glu Leu Asn Leu Gly Arg Arg
    610                 615                 620


Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Pro Glu
625                 630                 635                 640


Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                645                 650                 655


Glu Leu Gln Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
            660                 665                 670


Met Lys Gly Glu Arg Arg Arg Gly Gly Lys Gly His Asp Gly Leu Tyr
        675                 680                 685


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Ala Leu His
    690                 695                 700


Met Gln Ala Leu Pro Pro Arg
705                 710


<210> 515
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 515
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 Gln Gln Ser Gly Pro Glu Leu
```

```
            20                  25                  30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
```

225 230 235 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
245 250 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
260 265 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
275 280 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
290 295 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305 310 315 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
325 330 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
340 345 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp

435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 516
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 516
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

```
Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320
```

```
Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 517
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

chimeric antigen receptor

<400> 517
```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140


Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160


Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175


Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
```

```
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Met Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
305                 310                 315                 320

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
                325                 330                 335

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            340                 345                 350

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        355                 360                 365

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    370                 375                 380

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
385                 390                 395                 400

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
```

405 410 415

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
420 425 430

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
435 440 445

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
450 455 460

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
465 470 475 480

Leu Pro Pro Arg

<210> 518
<211> 476
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 518
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
50 55 60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65 70 75 80

```
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270

Pro Pro Cys Pro Pro Cys Pro Met Phe Trp Val Leu Val Val Val Gly
        275                 280                 285
```

```
Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
    290                 295                 300

Phe Trp Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
305                 310                 315                 320

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
                325                 330                 335

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
            340                 345                 350

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
        355                 360                 365

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
    370                 375                 380

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
385                 390                 395                 400

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
                405                 410                 415

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
            420                 425                 430

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
        435                 440                 445

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu Gly
    450                 455                 460

Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly
465                 470                 475
```

<210> 519
<211> 248
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 519
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 Lys Ala Gly Gly Gly
100 105 110

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser
130 135 140

Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp
145 150 155 160

Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp
165 170 175

Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu

180 185 190

Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe
195 200 205

Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys
210 215 220

Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly
225 230 235 240

Gln Gly Thr Ser Val Thr Val Ser
245

<210> 520
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 520
Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1 5 10 15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Asp Ile Tyr
20 25 30

Phe Asn Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Thr Asn Arg Leu Ala Asp Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Gln Tyr Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Tyr Lys Asn Tyr
85 90 95

```
Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ser Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Arg Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
    130                 135                 140

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
145                 150                 155                 160

Thr Leu Ser Asn Tyr Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys
                165                 170                 175

Gly Leu Glu Trp Val Ser Ser Ile Ser Leu Asn Gly Gly Ser Thr Tyr
            180                 185                 190

Tyr Arg Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
        195                 200                 205

Lys Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
    210                 215                 220

Ala Val Tyr Tyr Cys Ala Ala Gln Asp Ala Tyr Thr Gly Gly Tyr Phe
225                 230                 235                 240

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Met
                245                 250
```

<210> 521
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 521

```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
```

210 215 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Ser Val Thr Val Ser Ser Thr Arg Thr Thr Thr Pro Ala Pro Arg
260 265 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
275 280 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
290 295 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305 310 315 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Ala Val
325 330 335

Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr Gly Val
340 345 350

Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys Gln Phe Gln
355 360 365

Pro Tyr Phe Ile Pro Ile Asn Ser Ala Arg Val Lys Phe Ser Arg Ser
370 375 380

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385 390 395 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
405 410 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln

420 425 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
435 440 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
450 455 460

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465 470 475 480

Leu His Met Gln Ala Leu Pro Pro Arg
485

<210> 522
<211> 522
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 522
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

```
Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300
```

```
Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Ala Leu Tyr Leu
                325                 330                 335

Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly
            340                 345                 350

Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His
        355                 360                 365

Ser Thr Leu Ala Lys Ile Arg Ser Lys Arg Ser Arg Leu Leu His Ser
    370                 375                 380

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
385                 390                 395                 400

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly
                405                 410                 415

Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
            420                 425                 430

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
        435                 440                 445

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
    450                 455                 460

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
465                 470                 475                 480

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
                485                 490                 495

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
            500                 505                 510
```

Val Phe Asp Val Glu Leu Leu Lys Leu Glu
        515   520

<210> 523
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 523
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20   25   30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35   40   45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50   55   60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65   70   75   80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85   90   95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100   105   110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115   120   125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130   135   140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr

```
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Ala Leu Tyr Leu
                325                 330                 335

Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly
            340                 345                 350

Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His
```

355 360 365

Ser Thr Leu Ala Lys Ile Arg Ser Lys Arg Ser Arg Leu Leu His Ser
370 375 380

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
385 390 395 400

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Ile
405 410 415

Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg Leu
420 425 430

Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro
435 440 445

Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser
450 455 460

Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys
465 470 475 480

Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala Trp
485 490 495

Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys
500 505

<210> 524
<211> 528
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 524
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220
```

```
Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Gln Arg Arg Lys
                325                 330                 335

Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro Cys
            340                 345                 350

His Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln
        355                 360                 365

Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Arg Ser Lys Arg
    370                 375                 380

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
385                 390                 395                 400

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
                405                 410                 415

Ala Ala Tyr Arg Ser Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp
            420                 425                 430
```

Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr
435 440 445

Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn
450 455 460

Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp
465 470 475 480

Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr
485 490 495

Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile
500 505 510

Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu
515 520 525

<210> 525
<211> 514
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 525
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro

65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu

```
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Gln Arg Arg Lys
                325                 330                 335

Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro Cys
            340                 345                 350

His Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln
        355                 360                 365

Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Arg Ser Lys Arg
    370                 375                 380

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
385                 390                 395                 400

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
                405                 410                 415

Ala Ala Tyr Arg Ser Ile Leu Trp His Glu Met Trp His Glu Gly Leu
            420                 425                 430

Ile Glu Ala Ser Arg Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met
        435                 440                 445

Phe Glu Val Leu Glu Pro Leu His Ala Met Met Glu Arg Gly Pro Gln
    450                 455                 460

Thr Leu Lys Glu Thr Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met
465                 470                 475                 480

Glu Ala Gln Glu Trp Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys
```

485 490 495

Asp Leu Leu Gln Ala Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile
500 505 510

Ser Lys

<210> 526
<211> 522
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 526
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335
```

```
Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Ser Lys Arg Ser Arg Leu Leu His Ser
    370                 375                 380

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
385                 390                 395                 400

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly
                405                 410                 415

Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
            420                 425                 430

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
        435                 440                 445

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
    450                 455                 460

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
465                 470                 475                 480

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
                485                 490                 495

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
            500                 505                 510

Val Phe Asp Val Glu Leu Leu Lys Leu Glu
        515                 520
```

<210> 527
<211> 508
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 527
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly

```
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Ser Lys Arg Ser Arg Leu Leu His Ser
    370                 375                 380

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
```

385 390 395 400

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Ile
405 410 415

Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg Leu
420 425 430

Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu Pro
435 440 445

Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr Ser
450 455 460

Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp Cys
465 470 475 480

Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala Trp
485 490 495

Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys
500 505

<210> 528
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 528
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

```
Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255
```

```
Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460
```

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 529
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 529
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly

```
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
```

340 345 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 530
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 530
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

```
Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220
```

```
Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430
```

```
Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445


Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460


Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480


Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495


<210> 531
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 531
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15


Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30


Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
        35                  40                  45


Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60


Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80


Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95


Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
```

100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
165 170 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
180 185 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
195 200 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225 230 235 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
245 250 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
260 265 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
275 280 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
290 295 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile

305 310 315 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
325 330 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
340 345 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 532
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 532

```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                  10                  15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190
```

```
Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400
```

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 533
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 533
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr

```
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
```

```
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
```

485 490 495

<210> 534
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 534
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

```
Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365
```

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 535
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 535
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr

```
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
```

```
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
```

450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 536
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 536
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

```
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ala Ala
    130                 135                 140


Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg
145                 150                 155                 160


Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp
                165                 170                 175


Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met
            180                 185                 190


Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205


Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val
    210                 215                 220


Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly
225                 230                 235                 240


Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
                245                 250


<210> 537
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 537
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15


Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30


Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
```

```
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
```

245 250 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
260 265 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
275 280 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
290 295 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305 310 315 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
325 330 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
340 345 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg

450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 538
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 538
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

```
Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335
```

```
Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 539
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 539

```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
```

```
1               5                   10                  15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
            20                  25                  30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
        35                  40                  45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65                  70                  75                  80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
                85                  90                  95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
```

```
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
```

420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 540
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 540
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 Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65 70 75 80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
85 90 95

```
Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300
```

```
Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 541
<211> 495
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 541
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
165 170 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr

```
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
```

385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 542
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 542
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 Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
50 55 60

```
Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
            260                 265                 270
```

```
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480
```

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 543
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 543
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met

```
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
```

355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 544
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 544
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 Gln Gln Ser Gly Pro Glu Leu
20 25 30

```
Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240
```

```
Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445
```

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 545
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 545
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe

```
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145                 150                 155                 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
```

325 330 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
340 345 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
355 360 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
370 375 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 546
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 546

```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                  10                  15

Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
            20                  25                  30

Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
        35                  40                  45

Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
    50                  55                  60

Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn
            100                 105                 110

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Lys
        115                 120                 125

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu
145                 150                 155                 160

Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val
                165                 170                 175

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys
            180                 185                 190

Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
        195                 200                 205
```

```
Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys
    210                 215                 220

Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala
225                 230                 235                 240

Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
                245                 250                 255

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Asp Pro Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
385                 390                 395                 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415
```

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
420 425 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
435 440 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
450 455 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465 470 475 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 547
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 547
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
20 25 30

Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp
35 40 45

Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
50 55 60

Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser

85 90 95

Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn
100 105 110

Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Lys
115 120 125

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu
145 150 155 160

Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val
165 170 175

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys
180 185 190

Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
195 200 205

Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys
210 215 220

Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala
225 230 235 240

Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
245 250 255

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Asp Pro Thr
260 265 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
275 280 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly

```
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
385                 390                 395                 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 548

<211> 144
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 548
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

<210> 549
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

chimeric antigen receptor

<400> 549
```
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45


Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110


Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140


Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160


Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175


Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190


Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
```

195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp

405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 550
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 550
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

```
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 551
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 551
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145 150 155 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr

```
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
```

370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 552
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 552
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

```
Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255
```

```
Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
```

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 553
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 553
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

```
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
```

340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 554
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 554
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220
```

```
Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430
```

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435   440   445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450   455   460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465   470   475   480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485   490

<210> 555
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 555
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20   25   30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35   40   45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50   55   60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65   70   75   80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85   90   95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala

100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
165 170 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
180 185 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
245 250 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu

305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 556
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 556

```
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190
```

```
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400
```

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 557
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 557
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro

65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
165 170 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
180 185 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
195 200 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
210 215 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225 230 235 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
245 250 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu

```
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
```

485 490

<210> 558
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 558
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

```
Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365
```

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 559
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 559
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val

```
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
```

```
               245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
```

450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 560
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 560
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335
```

```
Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 561
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 561
```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
```

210 215 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu

420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 562
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 562
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 Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65 70 75 80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
85 90 95

```
Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300
```

```
Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 563
<211> 495
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 563
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile
20 25 30

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
35 40 45

Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr
65 70 75 80

Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser
85 90 95

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
100 105 110

Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
145 150 155 160

Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser
165 170 175

Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr

```
            180                 185                 190

Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro
                245                 250                 255

Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ser Asp Pro
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
```

385 390 395 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
405 410 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 564
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 564
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 Met Met Thr Gln Ser Pro Ser Ser Leu
20 25 30

Ala Val Ser Ala Gly Glu Lys Val Thr Met Thr Cys Lys Ser Ser Gln
35 40 45

Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
50 55 60

```
Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys His Gln Tyr Leu Ser Ser His Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Arg Tyr Trp Ile His Trp Val Lys Gln Arg Pro Ile Gln Gly Leu
            180                 185                 190

Glu Trp Ile Gly Asn Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn
        195                 200                 205

Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Gly
    210                 215                 220

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Thr Glu Asp Leu Tyr Tyr Ala Met Glu Tyr Trp Gly
                245                 250                 255

Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270
```

```
Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser
                325                 330                 335

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
            340                 345                 350

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
        355                 360                 365

Asp Phe Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr
    370                 375                 380

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
385                 390                 395                 400

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
                405                 410                 415

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
            420                 425                 430

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
        435                 440                 445

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
    450                 455                 460

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
465                 470                 475                 480
```

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
485 490 495

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
500 505 510

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
515 520 525

Pro Arg
530

<210> 565
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 565
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly

100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly

305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 566
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 566

```
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190
```

```
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400
```

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 567
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 567
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr

```
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
```

```
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
```

<210> 568
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 568
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

```
Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365
```

```
Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380


Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400


Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415


Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430


Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445


Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460


His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 569
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 569
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
```

```
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
```

```
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
```

450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 570
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 570
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

```
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335
```

```
Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 571
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 571

```
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
```

```
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
```

420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 572
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 572
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

```
Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300
```

```
Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 573
<211> 491
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 573
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
165 170 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly

```
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
```

385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 574
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 574
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

```
Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270
```

```
Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480
```

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 575
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 575
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr

```
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
```

355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 576
<211> 465
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 576
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Ala Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

```
Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Glu Asp Thr Asn
65                  70                  75                  80

Tyr Ser Gly Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser
                85                  90                  95

Ser Thr Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Phe Cys Ala Arg Ser Leu Leu Tyr Gly Asp Tyr Leu Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr
145                 150                 155                 160

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
                165                 170                 175

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln
            180                 185                 190

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
        195                 200                 205

Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser
    210                 215                 220

Tyr Phe Leu Thr Ile Asn Asn Met Glu Ala Glu Asp Ala Ala Thr Tyr
225                 230                 235                 240
```

```
Tyr Cys Gln Gln Trp Asn Ile Asn Pro Leu Thr Phe Gly Ala Gly Thr
                245                 250                 255

Lys Leu Glu Leu Lys Arg Ser Asp Pro Ala Glu Pro Lys Ser Pro Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Lys Asp Pro Lys Phe Trp Val
        275                 280                 285

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
    290                 295                 300

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu
305                 310                 315                 320

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
                325                 330                 335

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
            340                 345                 350

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
        355                 360                 365

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
    370                 375                 380

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
385                 390                 395                 400

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
                405                 410                 415

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
            420                 425                 430

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
        435                 440                 445
```

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
450 455 460

Arg
465

<210> 577
<211> 681
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 577
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Ala Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Glu Asp Thr Asn
65 70 75 80

Tyr Ser Gly Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Thr Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Leu Leu Tyr Gly Asp Tyr Leu Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly

130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr
145 150 155 160

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
165 170 175

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln
180 185 190

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
195 200 205

Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser
210 215 220

Tyr Phe Leu Thr Ile Asn Asn Met Glu Ala Glu Asp Ala Ala Thr Tyr
225 230 235 240

Tyr Cys Gln Gln Trp Asn Ile Asn Pro Leu Thr Phe Gly Ala Gly Thr
245 250 255

Lys Leu Glu Leu Lys Arg Ser Asp Pro Ala Glu Pro Lys Ser Pro Asp
260 265 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
275 280 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala
290 295 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
305 310 315 320

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
325 330 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

340 345 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
355 360 365

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
370 375 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385 390 395 400

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
405 410 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
420 425 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
435 440 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
450 455 460

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465 470 475 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
485 490 495

Lys Lys Asp Pro Lys Phe Trp Val Leu Val Val Val Gly Gly Val Leu
500 505 510

Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
515 520 525

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
530 535 540

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro

545 550 555 560

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
565 570 575

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
580 585 590

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
595 600 605

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
610 615 620

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
625 630 635 640

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
645 650 655

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
660 665 670

Leu His Met Gln Ala Leu Pro Pro Arg
675 680

<210> 578
<211> 838
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 578
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Ser Val Lys Glu Ser Glu Gly Asp Leu
20 25 30

```
Val Thr Pro Ala Gly Asn Leu Thr Leu Thr Cys Thr Ala Ser Gly Ser
        35                  40                  45

Asp Ile Asn Asp Tyr Pro Ile Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Phe Ile Asn Ser Gly Gly Ser Thr Trp Tyr
65                  70                  75                  80

Ala Ser Trp Val Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr
                85                  90                  95

Val Asp Leu Lys Met Thr Ser Leu Thr Thr Asp Asp Thr Ala Thr Tyr
            100                 105                 110

Phe Cys Ala Arg Gly Tyr Ser Thr Tyr Tyr Gly Asp Phe Asn Ile Trp
        115                 120                 125

Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr
145                 150                 155                 160

Pro Ser Ser Thr Ser Gly Ala Val Gly Gly Thr Val Thr Ile Asn Cys
                165                 170                 175

Gln Ala Ser Gln Ser Ile Asp Ser Asn Leu Ala Trp Phe Gln Gln Lys
            180                 185                 190

Pro Gly Gln Pro Pro Thr Leu Leu Ile Tyr Arg Ala Ser Asn Leu Ala
        195                 200                 205

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Glu Tyr
    210                 215                 220

Thr Leu Thr Ile Ser Gly Val Gln Arg Glu Asp Ala Ala Thr Tyr Tyr
225                 230                 235                 240
```

```
Cys Leu Gly Gly Val Gly Asn Val Ser Tyr Arg Thr Ser Phe Gly Gly
                245                 250                 255

Gly Thr Glu Val Val Val Lys Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            260                 265                 270

Pro Cys Pro Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
        275                 280                 285

Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys
    290                 295                 300

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
305                 310                 315                 320

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
                325                 330                 335

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
            340                 345                 350

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
        355                 360                 365

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
    370                 375                 380

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
385                 390                 395                 400

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
                405                 410                 415

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
            420                 425                 430

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
        435                 440                 445
```

```
Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly
    450                 455                 460

Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
465                 470                 475                 480

Arg Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His
                485                 490                 495

Pro Ala Phe Leu Leu Ile Pro Arg Lys Val Cys Asn Gly Ile Gly Ile
            500                 505                 510

Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His
        515                 520                 525

Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val
    530                 535                 540

Ala Phe Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln
545                 550                 555                 560

Glu Leu Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu
                565                 570                 575

Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn
            580                 585                 590

Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu
        595                 600                 605

Ala Val Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys
    610                 615                 620

Glu Ile Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys
625                 630                 635                 640

Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln
                645                 650                 655
```

```
Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr
            660                 665                 670

Gly Gln Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro
        675                 680                 685

Glu Pro Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu
    690                 695                 700

Cys Val Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val
705                 710                 715                 720

Glu Asn Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala
                725                 730                 735

Met Asn Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys
            740                 745                 750

Ala His Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly
        755                 760                 765

Val Met Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly
    770                 775                 780

His Val Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly
785                 790                 795                 800

Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile
                805                 810                 815

Ala Thr Gly Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu
            820                 825                 830

Gly Ile Gly Leu Phe Met
        835
```

<210> 579
<211> 1055
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 579
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Ser Val Lys Glu Ser Glu Gly Asp Leu
20 25 30

Val Thr Pro Ala Gly Asn Leu Thr Leu Thr Cys Thr Ala Ser Gly Ser
35 40 45

Asp Ile Asn Asp Tyr Pro Ile Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Phe Ile Asn Ser Gly Gly Ser Thr Trp Tyr
65 70 75 80

Ala Ser Trp Val Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr
85 90 95

Val Asp Leu Lys Met Thr Ser Leu Thr Thr Asp Asp Thr Ala Thr Tyr
100 105 110

Phe Cys Ala Arg Gly Tyr Ser Thr Tyr Tyr Gly Asp Phe Asn Ile Trp
115 120 125

Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr
145 150 155 160

Pro Ser Ser Thr Ser Gly Ala Val Gly Gly Thr Val Thr Ile Asn Cys
165 170 175

Gln Ala Ser Gln Ser Ile Asp Ser Asn Leu Ala Trp Phe Gln Gln Lys

```
            180                 185                 190

Pro Gly Gln Pro Pro Thr Leu Leu Ile Tyr Arg Ala Ser Asn Leu Ala
        195                 200                 205

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Glu Tyr
    210                 215                 220

Thr Leu Thr Ile Ser Gly Val Gln Arg Glu Asp Ala Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Leu Gly Gly Val Gly Asn Val Ser Tyr Arg Thr Ser Phe Gly Gly
                245                 250                 255

Gly Thr Glu Val Val Val Lys Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            260                 265                 270

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        275                 280                 285

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    290                 295                 300

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
305                 310                 315                 320

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                325                 330                 335

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            340                 345                 350

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        355                 360                 365

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    370                 375                 380

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
```

385 390 395 400

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
405 410 415

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
420 425 430

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
435 440 445

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
450 455 460

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
465 470 475 480

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Phe Trp Val
485 490 495

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
500 505 510

Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly Arg Lys Lys Leu Leu
515 520 525

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
530 535 540

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
545 550 555 560

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
565 570 575

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
580 585 590

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly

595 600 605

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
610 615 620

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
625 630 635 640

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
645 650 655

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
660 665 670

Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys
675 680 685

Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Leu Leu Leu Val Thr
690 695 700

Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe Leu Leu Ile Pro
705 710 715 720

Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu
725 730 735

Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile
740 745 750

Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe
755 760 765

Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr
770 775 780

Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn
785 790 795 800

Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg

805 810 815

Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile
820 825 830

Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val
835 840 845

Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp
850 855 860

Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn
865 870 875 880

Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu
885 890 895

Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser
900 905 910

Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu
915 920 925

Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln
930 935 940

Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly
945 950 955 960

Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro
965 970 975

His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr
980 985 990

Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His
995 1000 1005

Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys

1010 1015 1020

Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val
1025 1030 1035

Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu
1040 1045 1050

Phe Met
1055

<210> 580
<211> 945
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 580
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Ser Val Lys Glu Ser Glu Gly Asp Leu
20 25 30

Val Thr Pro Ala Gly Asn Leu Thr Leu Thr Cys Thr Ala Ser Gly Ser
35 40 45

Asp Ile Asn Asp Tyr Pro Ile Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Phe Ile Asn Ser Gly Gly Ser Thr Trp Tyr
65 70 75 80

Ala Ser Trp Val Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr
85 90 95

Val Asp Leu Lys Met Thr Ser Leu Thr Thr Asp Asp Thr Ala Thr Tyr
100 105 110

```
Phe Cys Ala Arg Gly Tyr Ser Thr Tyr Tyr Gly Asp Phe Asn Ile Trp
        115                 120                 125

Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Thr
145                 150                 155                 160

Pro Ser Ser Thr Ser Gly Ala Val Gly Gly Thr Val Thr Ile Asn Cys
                165                 170                 175

Gln Ala Ser Gln Ser Ile Asp Ser Asn Leu Ala Trp Phe Gln Gln Lys
            180                 185                 190

Pro Gly Gln Pro Pro Thr Leu Leu Ile Tyr Arg Ala Ser Asn Leu Ala
        195                 200                 205

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Glu Tyr
    210                 215                 220

Thr Leu Thr Ile Ser Gly Val Gln Arg Glu Asp Ala Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Leu Gly Gly Val Gly Asn Val Ser Tyr Arg Thr Ser Phe Gly Gly
                245                 250                 255

Gly Thr Glu Val Val Val Lys Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            260                 265                 270

Pro Cys Pro Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        275                 280                 285

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    290                 295                 300

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
305                 310                 315                 320
```

```
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                325                 330                 335

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
            340                 345                 350

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        355                 360                 365

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Phe
    370                 375                 380

Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu
385                 390                 395                 400

Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly Arg Lys Lys
                405                 410                 415

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            420                 425                 430

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        435                 440                 445

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    450                 455                 460

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
465                 470                 475                 480

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                485                 490                 495

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            500                 505                 510

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        515                 520                 525
```

```
Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    530                 535                 540

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
545                 550                 555                 560

Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu
                565                 570                 575

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Leu Leu Leu
            580                 585                 590

Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe Leu Leu
        595                 600                 605

Ile Pro Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp
    610                 615                 620

Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr
625                 630                 635                 640

Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp
                645                 650                 655

Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu
            660                 665                 670

Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro
        675                 680                 685

Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg
    690                 695                 700

Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu
705                 710                 715                 720

Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly
                725                 730                 735
```

```
Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile
            740                 745                 750

Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile
        755                 760                 765

Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His
    770                 775                 780

Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys
785                 790                 795                 800

Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys
                805                 810                 815

Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys
            820                 825                 830

Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys
        835                 840                 845

Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp
    850                 855                 860

Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn
865                 870                 875                 880

Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu
                885                 890                 895

Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly
            900                 905                 910

Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val
        915                 920                 925

Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe
    930                 935                 940
```

Met
945

<210> 581
<211> 845
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 581
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Glu Gln Leu Val Glu Ser Gly Gly Arg
20 25 30

Leu Val Thr Pro Gly Gly Ser Leu Thr Leu Ser Cys Lys Ala Ser Gly
35 40 45

Phe Asp Phe Ser Ala Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Ala Thr Ile Tyr Pro Ser Ser Gly Lys Thr
65 70 75 80

Tyr Tyr Ala Thr Trp Val Asn Gly Arg Phe Thr Ile Ser Ser Asp Asn
85 90 95

Ala Gln Asn Thr Val Asp Leu Gln Met Asn Ser Leu Thr Ala Ala Asp
100 105 110

Arg Ala Thr Tyr Phe Cys Ala Arg Asp Ser Tyr Ala Asp Asp Gly Ala
115 120 125

Leu Phe Asn Ile Trp Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu

```
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ser Val Ser Ala Ala Leu Gly Ser Pro Ala
                165                 170                 175

Lys Ile Thr Cys Thr Leu Ser Ser Ala His Lys Thr Asp Thr Ile Asp
            180                 185                 190

Trp Tyr Gln Gln Leu Gln Gly Glu Ala Pro Arg Tyr Leu Met Gln Val
        195                 200                 205

Gln Ser Asp Gly Ser Tyr Thr Lys Arg Pro Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Ser Ser Gly Ala Asp Arg Tyr Leu Ile Ile Pro Ser Val
225                 230                 235                 240

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Asp Tyr Ile Gly
                245                 250                 255

Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Thr Gly Glu Ser
            260                 265                 270

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Met Phe Trp Val Leu Val
        275                 280                 285

Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
    290                 295                 300

Phe Ile Ile Phe Trp Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
305                 310                 315                 320

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
                325                 330                 335

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
            340                 345                 350

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
```

```
        355                 360                 365

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
    370                 375                 380

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
385                 390                 395                 400

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
                405                 410                 415

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
            420                 425                 430

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
        435                 440                 445

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    450                 455                 460

Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp
465                 470                 475                 480

Val Glu Glu Asn Pro Gly Pro Arg Met Leu Leu Leu Val Thr Ser Leu
                485                 490                 495

Leu Leu Cys Glu Leu Pro His Pro Ala Phe Leu Leu Ile Pro Arg Lys
            500                 505                 510

Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile
        515                 520                 525

Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly
    530                 535                 540

Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His
545                 550                 555                 560

Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys
```

```
                565                 570                 575

Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr
            580                 585                 590

Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys
        595                 600                 605

Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser
    610                 615                 620

Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile
625                 630                 635                 640

Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys
                645                 650                 655

Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly
            660                 665                 670

Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser
        675                 680                 685

Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg
    690                 695                 700

Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu
705                 710                 715                 720

Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His
                725                 730                 735

Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly
            740                 745                 750

Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys
        755                 760                 765

Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val
```

770 775 780

Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn
785 790 795 800

Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn
805 810 815

Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu
820 825 830

Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met
835 840 845

<210> 582
<211> 952
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 582
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Glu Gln Leu Val Glu Ser Gly Gly Arg
20 25 30

Leu Val Thr Pro Gly Gly Ser Leu Thr Leu Ser Cys Lys Ala Ser Gly
35 40 45

Phe Asp Phe Ser Ala Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Ala Thr Ile Tyr Pro Ser Ser Gly Lys Thr
65 70 75 80

Tyr Tyr Ala Thr Trp Val Asn Gly Arg Phe Thr Ile Ser Ser Asp Asn
85 90 95

```
Ala Gln Asn Thr Val Asp Leu Gln Met Asn Ser Leu Thr Ala Ala Asp
            100                 105                 110

Arg Ala Thr Tyr Phe Cys Ala Arg Asp Ser Tyr Ala Asp Asp Gly Ala
        115                 120                 125

Leu Phe Asn Ile Trp Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ser Val Ser Ala Ala Leu Gly Ser Pro Ala
                165                 170                 175

Lys Ile Thr Cys Thr Leu Ser Ser Ala His Lys Thr Asp Thr Ile Asp
            180                 185                 190

Trp Tyr Gln Gln Leu Gln Gly Glu Ala Pro Arg Tyr Leu Met Gln Val
        195                 200                 205

Gln Ser Asp Gly Ser Tyr Thr Lys Arg Pro Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Ser Ser Gly Ala Asp Arg Tyr Leu Ile Ile Pro Ser Val
225                 230                 235                 240

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Asp Tyr Ile Gly
                245                 250                 255

Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Thr Gly Glu Ser
            260                 265                 270

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gln Pro Arg Glu Pro
        275                 280                 285

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    290                 295                 300
```

```
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
305                 310                 315                 320

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                325                 330                 335

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            340                 345                 350

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        355                 360                 365

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    370                 375                 380

Leu Ser Leu Gly Lys Met Phe Trp Val Leu Val Val Val Gly Gly Val
385                 390                 395                 400

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
                405                 410                 415

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            420                 425                 430

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        435                 440                 445

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    450                 455                 460

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
465                 470                 475                 480

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                485                 490                 495

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            500                 505                 510
```

```
Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        515                 520                 525

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    530                 535                 540

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
545                 550                 555                 560

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu Gly Gly Gly
                565                 570                 575

Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro
            580                 585                 590

Gly Pro Arg Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu
        595                 600                 605

Pro His Pro Ala Phe Leu Leu Ile Pro Arg Lys Val Cys Asn Gly Ile
    610                 615                 620

Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile
625                 630                 635                 640

Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu
                645                 650                 655

Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp
            660                 665                 670

Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe
        675                 680                 685

Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe
    690                 695                 700

Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe
705                 710                 715                 720
```

```
Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser
                725                 730                 735

Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn
            740                 745                 750

Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser
        755                 760                 765

Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys
    770                 775                 780

Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp
785                 790                 795                 800

Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly
                805                 810                 815

Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu
            820                 825                 830

Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro
        835                 840                 845

Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile
    850                 855                 860

Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro
865                 870                 875                 880

Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp
                885                 890                 895

Ala Gly His Val Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys
            900                 905                 910

Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro
        915                 920                 925
```

Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu Leu Leu Val Val
930 935 940

Ala Leu Gly Ile Gly Leu Phe Met
945 950

<210> 583
<211> 1062
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 583
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gln Glu Gln Leu Val Glu Ser Gly Gly Arg
20 25 30

Leu Val Thr Pro Gly Gly Ser Leu Thr Leu Ser Cys Lys Ala Ser Gly
35 40 45

Phe Asp Phe Ser Ala Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Ala Thr Ile Tyr Pro Ser Ser Gly Lys Thr
65 70 75 80

Tyr Tyr Ala Thr Trp Val Asn Gly Arg Phe Thr Ile Ser Ser Asp Asn
85 90 95

Ala Gln Asn Thr Val Asp Leu Gln Met Asn Ser Leu Thr Ala Ala Asp
100 105 110

Arg Ala Thr Tyr Phe Cys Ala Arg Asp Ser Tyr Ala Asp Asp Gly Ala
115 120 125

Leu Phe Asn Ile Trp Gly Pro Gly Thr Leu Val Thr Ile Ser Ser Gly

```
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ser Val Ser Ala Ala Leu Gly Ser Pro Ala
                165                 170                 175

Lys Ile Thr Cys Thr Leu Ser Ser Ala His Lys Thr Asp Thr Ile Asp
            180                 185                 190

Trp Tyr Gln Gln Leu Gln Gly Glu Ala Pro Arg Tyr Leu Met Gln Val
        195                 200                 205

Gln Ser Asp Gly Ser Tyr Thr Lys Arg Pro Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Ser Ser Gly Ala Asp Arg Tyr Leu Ile Ile Pro Ser Val
225                 230                 235                 240

Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Asp Tyr Ile Gly
                245                 250                 255

Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Thr Gly Glu Ser
            260                 265                 270

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
        275                 280                 285

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
    290                 295                 300

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
305                 310                 315                 320

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
                325                 330                 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
```

340 345 350

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
355 360 365

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
370 375 380

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
385 390 395 400

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
405 410 415

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
420 425 430

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
435 440 445

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
450 455 460

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
465 470 475 480

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
485 490 495

Leu Gly Lys Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
500 505 510

Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys
515 520 525

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
530 535 540

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro

```
545                 550                 555                 560

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
                565                 570                 575

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
            580                 585                 590

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
        595                 600                 605

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
    610                 615                 620

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
625                 630                 635                 640

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
                645                 650                 655

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
            660                 665                 670

Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly
        675                 680                 685

Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro
    690                 695                 700

Arg Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His
705                 710                 715                 720

Pro Ala Phe Leu Leu Ile Pro Arg Lys Val Cys Asn Gly Ile Gly Ile
                725                 730                 735

Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His
            740                 745                 750

Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val
```

```
        755                 760                 765

Ala Phe Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln
    770                 775                 780

Glu Leu Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu
785                 790                 795                 800

Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn
                805                 810                 815

Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu
            820                 825                 830

Ala Val Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys
        835                 840                 845

Glu Ile Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys
    850                 855                 860

Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln
865                 870                 875                 880

Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr
                885                 890                 895

Gly Gln Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro
            900                 905                 910

Glu Pro Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu
        915                 920                 925

Cys Val Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val
    930                 935                 940

Glu Asn Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala
945                 950                 955                 960

Met Asn Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys
```

965 970 975

Ala His Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly
980 985 990

Val Met Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly
995 1000 1005

His Val Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr
1010 1015 1020

Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro
1025 1030 1035

Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu Leu Leu Val
1040 1045 1050

Val Ala Leu Gly Ile Gly Leu Phe Met
1055 1060

<210> 584
<211> 502
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 584
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

```
Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65                  70                  75                  80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270
```

```
Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
            340                 345                 350

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
        355                 360                 365

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
    370                 375                 380

Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
385                 390                 395                 400

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
                405                 410                 415

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
            420                 425                 430

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
        435                 440                 445

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
    450                 455                 460

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
465                 470                 475                 480
```

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
485 490 495

Gln Ala Leu Pro Pro Arg
500

<210> 585
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 585
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65 70 75 80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
100 105 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
115 120 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser

```
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Phe Ser
```

340 345 350

Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
355 360 365

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
370 375 380

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
385 390 395 400

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
405 410 415

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
420 425 430

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
435 440 445

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
450 455 460

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
465 470 475 480

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
485 490 495

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
500 505

<210> 586
<211> 509
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 586

```
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
    50                  55                  60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65                  70                  75                  80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205
```

```
Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Gln Arg Arg
            340                 345                 350

Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro
        355                 360                 365

Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile
    370                 375                 380

Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Arg Val Lys
385                 390                 395                 400

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
                405                 410                 415
```

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
420 425 430

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
435 440 445

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
450 455 460

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
465 470 475 480

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
485 490 495

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
500 505

<210> 587
<211> 550
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 587
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile

```
65                  70                  75                  80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
```

```
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
            340                 345                 350

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
        355                 360                 365

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
    370                 375                 380

Phe Ala Ala Tyr Arg Ser Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly
385                 390                 395                 400

Glu Ser Pro Val Glu Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg
                405                 410                 415

Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro
            420                 425                 430

Glu Pro Ala Cys Ser Pro Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        435                 440                 445

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
    450                 455                 460

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
465                 470                 475                 480

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
```

485 490 495

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
500 505 510

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
515 520 525

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
530 535 540

Gln Ala Leu Pro Pro Arg
545 550

<210> 588
<211> 556
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 588
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65 70 75 80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

```
Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300
```

```
Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Gln Arg Arg
            340                 345                 350

Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro
        355                 360                 365

Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile
    370                 375                 380

Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Arg Phe Ser
385                 390                 395                 400

Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
                405                 410                 415

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
            420                 425                 430

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
        435                 440                 445

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
    450                 455                 460

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
465                 470                 475                 480

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
                485                 490                 495

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
            500                 505                 510
```

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
515 520 525

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
530 535 540

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
545 550 555

<210> 589
<211> 506
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 589
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
50 55 60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
100 105 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile

```
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
            260                 265                 270

Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
        275                 280                 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    290                 295                 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305                 310                 315                 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
```

325 330 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
340 345 350

Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
355 360 365

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
370 375 380

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
385 390 395 400

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
405 410 415

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
420 425 430

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
435 440 445

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
450 455 460

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
465 470 475 480

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
485 490 495

Ala Leu His Met Gln Ala Leu Pro Pro Arg
500 505

<210> 590
<211> 560
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 590

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20                  25                  30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190
```

```
Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
            260                 265                 270

Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
        275                 280                 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    290                 295                 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305                 310                 315                 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
                325                 330                 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
            340                 345                 350

Asn Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu
        355                 360                 365

Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser
    370                 375                 380

Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser
385                 390                 395                 400
```

Pro Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
405 410 415

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
420 425 430

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
435 440 445

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
450 455 460

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
465 470 475 480

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
485 490 495

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
500 505 510

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
515 520 525

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
530 535 540

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
545 550 555 560

<210> 591
<211> 513
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 591
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro

```
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20                  25                  30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
```

210 215 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225 230 235 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
245 250 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
260 265 270

Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
275 280 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
290 295 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305 310 315 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
325 330 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
340 345 350

Asn Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu
355 360 365

Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser
370 375 380

Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser
385 390 395 400

Pro Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
405 410 415

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu

420 425 430

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
435 440 445

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
450 455 460

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
465 470 475 480

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
485 490 495

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
500 505 510

Arg

<210> 592
<211> 554
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 592
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
50 55 60

```
Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
            260                 265                 270
```

```
Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
        275                 280                 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    290                 295                 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305                 310                 315                 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
                325                 330                 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
            340                 345                 350

Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
        355                 360                 365

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
    370                 375                 380

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gln Arg Arg Lys Tyr Arg
385                 390                 395                 400

Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro Cys Arg Tyr
                405                 410                 415

Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp
            420                 425                 430

Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Arg Val Lys Phe Ser Arg
        435                 440                 445

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
    450                 455                 460

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
465                 470                 475                 480
```

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
485 490 495

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
500 505 510

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
515 520 525

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
530 535 540

Ala Leu His Met Gln Ala Leu Pro Pro Arg
545 550

<210> 593
<211> 476
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 593
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65 70 75 80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

85 90 95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
100 105 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
115 120 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
130 135 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145 150 155 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
165 170 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
180 185 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
195 200 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
210 215 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225 230 235 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
245 250 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
260 265 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
275 280 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg

290 295 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305 310 315 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
325 330 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
340 345 350

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
355 360 365

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
370 375 380

Phe Ala Ala Tyr Arg Ser Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly
385 390 395 400

Glu Ser Pro Val Glu Pro Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg
405 410 415

Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro
420 425 430

Glu Pro Ala Cys Ser Pro Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr
435 440 445

Glu Lys Ser Asp Gly Val Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu
450 455 460

Thr Tyr Glu Thr Leu Lys His Glu Lys Pro Pro Gln
465 470 475

<210> 594
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 594

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20                  25                  30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190
```

```
Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
            260                 265                 270

Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
        275                 280                 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    290                 295                 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305                 310                 315                 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
                325                 330                 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
            340                 345                 350

Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
        355                 360                 365

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
    370                 375                 380

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gln Arg Arg Lys Tyr Arg
385                 390                 395                 400
```

Ser Asn Lys Gly Glu Ser Pro Val Glu Pro Ala Glu Pro Cys Arg Tyr
405 410 415

Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr Ile Pro Ile Gln Glu Asp
420 425 430

Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro Gln Val Arg Lys Ala Ala
435 440 445

Ile Thr Ser Tyr Glu Lys Ser Asp Gly Val Tyr Thr Gly Leu Ser Thr
450 455 460

Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys His Glu Lys Pro Pro Gln
465 470 475 480

<210> 595
<211> 428
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 595
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 Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
65 70 75 80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

```
                85                  90                  95

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Gly Ser Ser Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Asp Ser Gly Gly Thr Phe
                165                 170                 175

Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Thr Asn Tyr Ala
        195                 200                 205

Gln Gln Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser
    210                 215                 220

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Glu Ala Val Ala Ala Asp Trp Leu Asp Pro Trp
                245                 250                 255

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Phe Val Pro Val Phe Leu
            260                 265                 270

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
```

290 295 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305 310 315 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
325 330 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
340 345 350

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
355 360 365

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
370 375 380

Phe Ala Ala Tyr Arg Ser Gln Val Arg Lys Ala Ala Ile Thr Ser Tyr
385 390 395 400

Glu Lys Ser Asp Gly Val Tyr Thr Gly Leu Ser Thr Arg Asn Gln Glu
405 410 415

Thr Tyr Glu Thr Leu Lys His Glu Lys Pro Pro Gln
420 425

<210> 596
<211> 432
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 596
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
20 25 30

```
Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240
```

```
Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ala Ala Phe Val
            260                 265                 270

Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro
        275                 280                 285

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    290                 295                 300

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
305                 310                 315                 320

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
                325                 330                 335

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
            340                 345                 350

Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
        355                 360                 365

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
    370                 375                 380

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gln Val Arg Lys Ala Ala
385                 390                 395                 400

Ile Thr Ser Tyr Glu Lys Ser Asp Gly Val Tyr Thr Gly Leu Ser Thr
                405                 410                 415

Arg Asn Gln Glu Thr Tyr Glu Thr Leu Lys His Glu Lys Pro Pro Gln
            420                 425                 430
```

<210> 597
<211> 486
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 597
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly

```
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
```

385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 598
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 598
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

```
Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480
```

Gln Ala Leu Pro Pro Arg
485

<210> 599
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 599
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met

```
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
```

355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 600
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 600
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

```
Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240
```

```
Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445
```

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 601
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 601
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

```
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
```

325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 602
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 602

```
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
        195                 200                 205
```

```
Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415
```

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 603
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 603
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys

85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
165 170 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
180 185 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
245 250 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His

290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 604

<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 604

```
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30


Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45


Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80


Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95


Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110


Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125


Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160


Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175
```

```
Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380
```

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 605
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 605
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala

```
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
```

```
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
```

465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 606
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 606
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

```
Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350
```

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 607
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 607
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu

```
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
```

225 230 235 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
245 250 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu

435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 608
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 608
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

```
Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320
```

```
Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 609
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

chimeric antigen receptor

<400> 609
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145 150 155 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser

195 200 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
210 215 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp

405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 610
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 610
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

```
Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 611
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 611
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly

```
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
```

370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 612
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 612
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

```
Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255
```

```
Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
```

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 613
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 613
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly

130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145 150 155 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
195 200 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln

340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 614
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 614
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220
```

```
Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430
```

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435   440   445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450   455   460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465   470   475   480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485   490

<210> 615
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      chimeric antigen receptor

<400> 615
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20   25   30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35   40   45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50   55   60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65   70   75   80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85   90   95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly

100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
165 170 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
180 185 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
195 200 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
210 215 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225 230 235 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
245 250 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu

305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 616
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 616

```
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190
```

```
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400
```

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 617
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 617
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr

```
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
```

```
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
```

485 490

<210> 618
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 618
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145 150 155 160

```
Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365
```

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 619
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 619
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln

```
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
```

245 250 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly

450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 620
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 620
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 Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

```
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335
```

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 621
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
chimeric antigen receptor

<400> 621
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 Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
```

210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu

420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 622
<211> 527
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 622
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 Arg
                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 Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr
                245                 250                 255

Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys
            260                 265                 270

His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp
        275                 280                 285

Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val
    290                 295                 300
```

```
Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu
305                 310                 315                 320

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
                325                 330                 335

Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
            340                 345                 350

Arg Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Lys Ser
        355                 360                 365

Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala
    370                 375                 380

Leu Pro Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn
385                 390                 395                 400

Cys Ser His His Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg
                405                 410                 415

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
            420                 425                 430

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
        435                 440                 445

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
    450                 455                 460

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
465                 470                 475                 480

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
                485                 490                 495

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
            500                 505                 510
```

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
515 520 525

<210> 623
<211> 527
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic chimeric antigen receptor

<400> 623
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Ala Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ala Phe Ser Ser Ser Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Glu Asp Thr Asn
65 70 75 80

Tyr Ser Gly Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser
85 90 95

Ser Thr Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser
100 105 110

Ala Val Tyr Phe Cys Ala Arg Ser Leu Leu Tyr Gly Asp Tyr Leu Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Val Leu Thr

145 150 155 160

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
165 170 175

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln
180 185 190

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
195 200 205

Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser
210 215 220

Tyr Phe Leu Thr Ile Asn Asn Met Glu Ala Glu Asp Ala Ala Thr Tyr
225 230 235 240

Tyr Cys Gln Gln Trp Asn Ile Asn Pro Leu Thr Phe Gly Ala Gly Thr
245 250 255

Lys Leu Glu Leu Lys Arg Ser Asp Pro Thr Thr Thr Pro Ala Pro Arg
260 265 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
275 280 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
290 295 300

Leu Asp Phe Ala Cys Asp Ile Phe Trp Val Leu Val Val Val Gly Gly
305 310 315 320

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
325 330 335

Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
340 345 350

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr

355 360 365

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Asp Gln Arg Leu
370 375 380

Pro Pro Asp Ala His Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro
385 390 395 400

Ile Gln Glu Glu Gln Ala Asp Ala His Ser Thr Leu Ala Lys Ile Arg
405 410 415

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
420 425 430

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
435 440 445

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
450 455 460

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
465 470 475 480

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
485 490 495

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
500 505 510

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
515 520 525

<210> 624
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 624

```
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 Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile
            180                 185                 190

Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln
        195                 200                 205
```

Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
210 215 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val
225 230 235 240

Ser Ser

<210> 625
<211> 69
<212> PRT
<213> Homo sapiens

<400> 625
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 Ile Tyr Ile
35 40 45

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
50 55 60

Ile Thr Leu Tyr Cys
65

<210> 626
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 626
gacatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 60

atcagttgca gggcaagtca ggacattagt aaatatttaa attggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctaccat acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggtaatacgc ttccgtacac gttcggaggg 300

gggaccaagc tggagatcac aggtggcggt ggctcgggcg gtggtgggtc gggtggcggc 360

ggatctgagg tgaaactgca ggagtcagga cctggcctgg tggcgccctc acagagcctg 420

tccgtcacat gcactgtctc aggggtctca ttacccgact atggtgtaag ctggattcgc 480

cagcctccac gaaagggtct ggagtggctg ggagtaatat ggggtagtga aaccacatac 540

tataattcag ctctcaaatc cagactgacc atcatcaagg acaactccaa gagccaagtt 600

ttcttaaaaa tgaacagtct gcaaactgat gacacagcca tttactactg tgccaaacat 660

tattactacg gtggtagcta tgctatggac tactggggcc aaggaacctc agtcaccgtc 720

tcctca 726

<210> 627
<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 627
accacaaccc cagcacctcg cccaccaaca ccagcaccaa ccatcgcatc ccagccactg 60

tctctgaggc ccgaggcatg taggcctgca gcaggaggcg ccgtgcacac caggggcctg 120

gactttgcct gcgatatcta tatctgggca ccactggcag gaacatgtgg cgtgctgctg 180

ctgtccctgg tcatcaccct gtattgc 207

<210> 628
<211> 21
<212> PRT
<213> Homo sapiens

<400> 628
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> 629
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      linker sequence

<400> 629
Gly Gly Ser Gly Gly
1   5

<210> 630
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      cleavage site

<400> 630
Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys
1   5   10

<210> 631
<211> 143
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 631
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1   5   10   15

His Ser Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Asn Trp Val Asn Val
            20   25   30

Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile

35 40 45

Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
50 55 60

Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu
65 70 75 80

Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu
85 90 95

Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys
100 105 110

Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln
115 120 125

Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Gly Ser
130 135 140

<210> 632
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 632
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagagct ccgaggtgct gggaagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatttgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gcggtgcgag gccaagaatt atagcggccg gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtctag ccggggctcc 420

tctgacccac agggagtgac atgcggagca gccaccctgt ccgccgagcg ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tcctgcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacaagct ccttctttat cagggacatc atcaagcctg atccccctaa gaacctgcag 660

ctgaagccac tgaagaattc tcgccaggtg gaggtgagct gggagtaccc agacacctgg 720

tccacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagtccaag 780

cgggagaaga aggacagagt gttcaccgat aagacatctg ccaccgtgat ctgtcggaag 840

aacgcctcca tctctgtgag ggcccaggat cgctactatt ctagctcctg gagcgagtgg 900

gcatccgtgc catgttct 918

<210> 633
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 633
atctgggagc tcaagaaaga cgtgtacgtg gtggaactgg actggtaccc cgacgcccct 60

ggcgaaatgg tggtgctgac atgcgacacc cctgaggagg atggcattac ctggaccctc 120

gatcagagct ccgaggtgct gggcagcggc aaaaccctga ccatccaggt gaaggagttt 180

ggcgatgccg gccagtacac atgtcacaag ggcggcgagg tgctgagcca ctccctgctg 240

ctgctccaca agaaggaaga tggcatctgg agcaccgaca ttctgaagga tcagaaggag 300

cccaagaaca agacattcct gaggtgtgag gccaagaact acagcggcag gtttacctgc 360

tggtggctga caacaatcag caccgacctc acattctccg tcaagtcctc caggggttct 420

tccgaccctc aaggcgtgac atgcggcgct gccaccctga gcgctgagag agtcaggggc 480

gacaacaagg agtacgagta cagcgtcgaa tgtcaggagg acagcgcctg tcccgccgct 540

gaagagagcc tgcctatcga ggtgatggtg gacgccgtgc acaaactgaa gtatgagaat 600

tacacctcca gcttcttcat cagggacatc atcaaacccg atcccccaa gaacctgcag 660

ctgaagcctc tgaagaacag cagacaggtc gaagtgtcct gggagtaccc tgatacctgg 720

tccacacccc acagctactt cagcctgacc ttttgcgtgc aggtgcaggg caagagcaaa 780

agggagaaga aggacagggt gtttaccgac aagacctccg ccacagtgat ttgcagaaag 840

aacgcctcca tcagcgtgag ggcccaggac aggtattaca gcagctcctg gagcgaatgg 900

gctagcgtgc cctgtagc 918

<210> 634
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 634
atctgggagc tcaagaaaga cgtgtacgtg gtggaactgg actggtaccc cgacgcccct 60

ggcgaaatgg tggtgctgac atgcgacacc cctgaggagg atggcattac ctggaccctc 120

gatcagagct ccgaggtgct gggcagcggc aaaaccctga ccatccaggt gaaggagttt 180

ggcgatgccg gccagtacac atgtcacaag ggcggcgagg tgctgagcca ctccctgctg 240

ctgctccaca agaaggaaga tggcatctgg agcaccgaca ttctgaagga tcagaaggag 300

cccaagaaca agacattcct gaggtgtgag gccaagaact acagcggcag gtttacctgc 360

tggtggctga caacaatcag caccgacctc acattctccg tcaagtcctc caggggttct 420

tccgaccctc aaggcgtgac atgcggcgct gccaccctga gcgctgagag agtcaggggc 480

gacaacaagg agtacgagta cagcgtcgaa tgtcaggagg acagcgcctg tcccgccgct 540

gaagagagcc tgcctatcga ggtgatggtg gacgccgtgc acaaactgaa gtatgagaat 600

tacacctcca gcttcttcat cagggacatc atcaaacccg atccccccaa gaacctgcag 660

ctgaagcctc tgaagaacag cagacaggtc gaagtgtcct gggagtaccc tgatacctgg 720

tccacacccc acagctactt cagcctgacc ttttgcgtgc aggtgcaggg caagagcaaa 780

agggagaaga aggacagggt gtttaccgac aagacctccg ccacagtgat ttgcagaaag 840

aacgcctcca tcagcgtgag ggcccaggac aggtattaca gcagctcctg gagcgaatgg 900

gctagcgtgc cctgtagc 918

<210> 635
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 635

```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175
```

```
Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380
```

```
Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 636
<211> 593
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 636
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255
```

```
Thr Ser Val Thr Val Ser Ser Gly Val Gln Val Glu Thr Ile Ser Pro
            260                 265                 270

Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His
        275                 280                 285

Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp
    290                 295                 300

Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg
305                 310                 315                 320

Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys
                325                 330                 335

Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly
            340                 345                 350

Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys
        355                 360                 365

Pro Glu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
    370                 375                 380

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
385                 390                 395                 400

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
                405                 410                 415

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
            420                 425                 430

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        435                 440                 445

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    450                 455                 460
```

```
Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
465                 470                 475                 480


Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
                485                 490                 495


Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
            500                 505                 510


Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
        515                 520                 525


Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
    530                 535                 540


Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
545                 550                 555                 560


Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
                565                 570                 575


Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
            580                 585                 590


Arg
```

<210> 637
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 637

```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240
```

```
His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Ile Ser Leu Ile Ala Ala Leu Ala Val
            260                 265                 270

Asp Tyr Val Ile Gly Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala
        275                 280                 285

Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met
    290                 295                 300

Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys
305                 310                 315                 320

Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp
                325                 330                 335

Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu
            340                 345                 350

Ile Met Val Ile Gly Gly Gly Arg Val Ile Glu Gln Phe Leu Pro Lys
        355                 360                 365

Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp
    370                 375                 380

Thr His Phe Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser Val Phe Ser
385                 390                 395                 400

Glu Phe His Asp Ala Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu
                405                 410                 415

Ile Leu Glu Arg Arg Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            420                 425                 430

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        435                 440                 445
```

```
Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
    450                 455                 460

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
465                 470                 475                 480

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
                485                 490                 495

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            500                 505                 510

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        515                 520                 525

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    530                 535                 540

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
545                 550                 555                 560

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                565                 570                 575

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            580                 585                 590

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        595                 600                 605

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    610                 615                 620

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
625                 630                 635                 640

Leu Pro Pro Arg
```

<210> 638
<211> 593
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 638
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145 150 155 160

```
Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly
305                 310                 315                 320

Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly
                325                 330                 335

Met Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys
            340                 345                 350

Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu
        355                 360                 365
```

```
Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile
    370                 375                 380

Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro
385                 390                 395                 400

Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Pro Glu Ile
                405                 410                 415

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
            420                 425                 430

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        435                 440                 445

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    450                 455                 460

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
465                 470                 475                 480

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
                485                 490                 495

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
            500                 505                 510

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
        515                 520                 525

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
    530                 535                 540

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
545                 550                 555                 560

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
                565                 570                 575
```

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
580 585 590

Arg

<210> 639
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 639
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

```
Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val
305                 310                 315                 320

Ile Gly Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala
                325                 330                 335

Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met Gly Arg His
            340                 345                 350
```

```
Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile
        355                 360                 365

Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser
    370                 375                 380

Val Asp Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val
385                 390                 395                 400

Ile Gly Gly Gly Arg Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys
                405                 410                 415

Leu Tyr Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe
            420                 425                 430

Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His
        435                 440                 445

Asp Ala Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu
    450                 455                 460

Arg Arg Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
465                 470                 475                 480

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
                485                 490                 495

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            500                 505                 510

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        515                 520                 525

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    530                 535                 540

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
545                 550                 555                 560
```

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
565 570 575

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
580 585 590

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
595 600 605

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
610 615 620

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
625 630 635 640

Leu Pro Pro Arg

<210> 640
<211> 649
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 640
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480
```

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Ile Ser Leu Ile Ala
485 490 495

Ala Leu Ala Val Asp His Val Ile Gly Met Glu Asn Ala Met Pro Trp
500 505 510

Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys
515 520 525

Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu
530 535 540

Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp
545 550 555 560

Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly
565 570 575

Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Tyr Glu Gln
580 585 590

Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu
595 600 605

Val Glu Gly Asp Thr His Phe Pro Asp Tyr Lys Pro Asp Asp Trp Glu
610 615 620

Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser His Ser
625 630 635 640

Tyr Cys Phe Glu Ile Leu Glu Arg Arg
645

<210> 641
<211> 598
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 641
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130   135   140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145   150   155   160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165   170   175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180   185   190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195   200   205

```
Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415
```

```
Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Gly Val Gln Val Glu
                485                 490                 495

Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr
            500                 505                 510

Cys Val Val His Tyr Thr Gly Met Leu Gly Asp Gly Lys Lys Val Asp
        515                 520                 525

Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln
    530                 535                 540

Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly
545                 550                 555                 560

Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr
                565                 570                 575

Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val
            580                 585                 590

Glu Leu Leu Glu Leu Glu
        595
```

<210> 642
<211> 677

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 642

```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175
```

```
Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380
```

```
Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Val Gly Ser Leu Asn
                485                 490                 495

Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp
            500                 505                 510

Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met
        515                 520                 525

Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly
    530                 535                 540

Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly
545                 550                 555                 560

Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly
                565                 570                 575

Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu
            580                 585                 590
```

Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly
595 600 605

Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly His Leu Lys Leu
610 615 620

Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro
625 630 635 640

Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val
645 650 655

Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val
660 665 670

Tyr Glu Lys Asn Asp
675

<210> 643
<211> 677
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 643
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Val Gly Ser Leu Asn
                485                 490                 495
```

```
Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp
            500                 505                 510

Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met
        515                 520                 525

Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly
    530                 535                 540

Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly
545                 550                 555                 560

Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly
                565                 570                 575

Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu
            580                 585                 590

Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly
        595                 600                 605

Ser Ser Val Ile Lys Glu Phe Met Asn His Pro Gly His Leu Lys Leu
    610                 615                 620

Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro
625                 630                 635                 640

Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val
                645                 650                 655

Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val
            660                 665                 670

Tyr Glu Lys Asn Asp
        675
```

<210> 644
<211> 677

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 644
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145 150 155 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

```
Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380
```

```
Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Val Gly Ser Leu Asn
                485                 490                 495


Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp
            500                 505                 510


Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Lys Arg Met
        515                 520                 525


Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly
    530                 535                 540


Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly
545                 550                 555                 560


Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly
                565                 570                 575


Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu
            580                 585                 590
```

Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly
595 600 605

Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly His Leu Lys Leu
610 615 620

Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro
625 630 635 640

Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val
645 650 655

Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val
660 665 670

Tyr Glu Lys Asn Asp
675

<210> 645
<211> 677
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 645
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Val Gly Ser Leu Asn
                485                 490                 495
```

```
Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp
            500                 505                 510

Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Phe Arg Met
        515                 520                 525

Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly
    530                 535                 540

Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Phe Arg Pro Leu Lys Gly
545                 550                 555                 560

Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly
                565                 570                 575

Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu
            580                 585                 590

Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly
        595                 600                 605

Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly His Leu Lys Leu
    610                 615                 620

Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro
625                 630                 635                 640

Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val
                645                 650                 655

Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val
            660                 665                 670

Tyr Glu Lys Asn Asp
        675
```

<210> 646
<211> 607

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 646

```
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 Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro
            20                  25                  30

Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His
        35                  40                  45

Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp
    50                  55                  60

Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg
65                  70                  75                  80

Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys
                85                  90                  95

Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly
            100                 105                 110

Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys
        115                 120                 125

Pro Glu Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys Asp Ile
    130                 135                 140

Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg
145                 150                 155                 160

Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn
                165                 170                 175
```

```
Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His
            180                 185                 190

Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
        195                 200                 205

Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp
    210                 215                 220

Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly Gly
                245                 250                 255

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly
            260                 265                 270

Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val
        275                 280                 285

Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro
    290                 295                 300

Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr
305                 310                 315                 320

Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp
                325                 330                 335

Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp
            340                 345                 350

Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser
        355                 360                 365

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    370                 375                 380
```

```
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
385                 390                 395                 400


Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
                405                 410                 415


Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
            420                 425                 430


Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
        435                 440                 445


Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
    450                 455                 460


Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
465                 470                 475                 480


Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
                485                 490                 495


Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
            500                 505                 510


Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
        515                 520                 525


Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
    530                 535                 540


Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
545                 550                 555                 560


Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
                565                 570                 575


Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
            580                 585                 590
```

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
595 600 605

<210> 647
<211> 658
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 647
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 Ser Gly Ile Ser Leu Ile Ala Ala Leu Ala Val
20 25 30

Asp Tyr Val Ile Gly Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala
35 40 45

Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met
50 55 60

Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys
65 70 75 80

Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp
85 90 95

Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu
100 105 110

Ile Met Val Ile Gly Gly Gly Arg Val Ile Glu Gln Phe Leu Pro Lys
115 120 125

Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp
130 135 140

Thr His Phe Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser Val Phe Ser
145 150 155 160

```
Glu Phe His Asp Ala Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu
                165                 170                 175

Ile Leu Glu Arg Arg Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser
            180                 185                 190

Lys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
        195                 200                 205

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
    210                 215                 220

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
225                 230                 235                 240

Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser
                245                 250                 255

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
            260                 265                 270

Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
        275                 280                 285

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly
    290                 295                 300

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln
305                 310                 315                 320

Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr
                325                 330                 335

Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile
            340                 345                 350

Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly
        355                 360                 365
```

```
Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile
    370                 375                 380

Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu
385                 390                 395                 400

Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr
                405                 410                 415

Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
            420                 425                 430

Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        435                 440                 445

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    450                 455                 460

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
465                 470                 475                 480

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                485                 490                 495

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
            500                 505                 510

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
        515                 520                 525

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
    530                 535                 540

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
545                 550                 555                 560

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
                565                 570                 575
```

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
580 585 590

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
595 600 605

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
610 615 620

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
625 630 635 640

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
645 650 655

Pro Arg

<210> 648
<211> 686
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 648
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 Ser Gly Val Gly Ser Leu Asn Cys Ile Val Ala
20 25 30

Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro
35 40 45

Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser
50 55 60

```
Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp
65                  70                  75                  80

Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu
                85                  90                  95

Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu
            100                 105                 110

Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu
        115                 120                 125

Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile
    130                 135                 140

Lys Glu Phe Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg
145                 150                 155                 160

Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu
                165                 170                 175

Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val
            180                 185                 190

Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn
        195                 200                 205

Asp Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys Asp Ile Gln
    210                 215                 220

Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
225                 230                 235                 240

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp
                245                 250                 255

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His Thr
            260                 265                 270
```

```
Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
        275                 280                 285

Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
    290                 295                 300

Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly
305                 310                 315                 320

Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly Gly Gly
                325                 330                 335

Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly Pro
            340                 345                 350

Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser
        355                 360                 365

Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro
    370                 375                 380

Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr
385                 390                 395                 400

Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn
                405                 410                 415

Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp
            420                 425                 430

Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr
        435                 440                 445

Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Thr
    450                 455                 460

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
465                 470                 475                 480
```

```
Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
                485                 490                 495

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
            500                 505                 510

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
        515                 520                 525

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
    530                 535                 540

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
545                 550                 555                 560

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
                565                 570                 575

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
            580                 585                 590

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
        595                 600                 605

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
    610                 615                 620

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
625                 630                 635                 640

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
                645                 650                 655

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
            660                 665                 670

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
        675                 680                 685
```

<210> 649
<211> 686
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 649

```
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 Ser Gly Val Gly Ser Leu Asn Cys Ile Val Ala
            20                  25                  30

Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro
        35                  40                  45

Pro Leu Arg Asn Glu Phe Arg Tyr Phe Lys Arg Met Thr Thr Thr Ser
    50                  55                  60

Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp
65                  70                  75                  80

Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu
                85                  90                  95

Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu
            100                 105                 110

Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu
        115                 120                 125

Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile
    130                 135                 140

Lys Glu Ala Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg
145                 150                 155                 160

Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu
                165                 170                 175
```

```
Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val
            180                 185                 190

Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn
        195                 200                 205

Asp Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys Asp Ile Gln
    210                 215                 220

Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
225                 230                 235                 240

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp
                245                 250                 255

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His Thr
            260                 265                 270

Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
        275                 280                 285

Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
    290                 295                 300

Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly
305                 310                 315                 320

Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly Gly Gly
                325                 330                 335

Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly Pro
            340                 345                 350

Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser
        355                 360                 365

Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro
    370                 375                 380
```

```
Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr
385                 390                 395                 400

Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn
                405                 410                 415

Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp
            420                 425                 430

Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr
        435                 440                 445

Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Thr
    450                 455                 460

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
465                 470                 475                 480

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
                485                 490                 495

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
            500                 505                 510

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
        515                 520                 525

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
    530                 535                 540

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
545                 550                 555                 560

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
                565                 570                 575

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
            580                 585                 590
```

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
595 600 605

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
610 615 620

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
625 630 635 640

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
645 650 655

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
660 665 670

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
675 680 685

<210> 650
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 650
gacatccaga tgacacagac cacaagctcc ctgtccgcct ctctgggcga cagagtgacc 60

atcagctgcc gggcctccca ggatatctct aagtatctga actggtacca gcagaagccc 120

gatggcacag tgaagctgct gatctatcac accagccgcc tgcactccgg agtgccttct 180

aggttcagcg gctccggctc tggcacagac tacagcctga ccatctccaa cctggagcag 240

gaggatatcg ccacctattt ctgccagcag ggcaatacac tgccttacac ctttggcggc 300

ggcacaaagc tggagatcac cggaggagga ggcagcggag gaggaggctc cggcggcggc 360

ggctctgagg tgaagctgca ggagtccgga ccaggcctgg tggcacctag ccagtccctg 420

tctgtgacat gtaccgtgtc cggcgtgtct ctgccagact acggcgtgtc ttggatcagg 480

cagccaccta ggaagggcct ggagtggctg ggcgtgatct ggggcagcga gacaacatac 540

tataattctg ccctgaagag cagactgaca atcatcaagg acaacagcaa gtcccaggtg 600

ttcctgaaga tgaatagcct gcagacagac gataccgcca tctactattg cgccaagcac 660

tactattacg gcggcagcta tgccatggat tactggggcc agggcacatc cgtgaccgtg 720

tctagc 726

<210> 651
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 651
gacatccaga tgacacagac cacaagctcc ctgagcgcct ccctgggcga cagagtgacc 60

atctcttgcc gggccagcca ggatatctcc aagtatctga actggtacca gcagaagccc 120

gatggcacag tgaagctgct gatctatcac acctctcgcc tgcacagcgg cgtgccttcc 180

aggttctctg gcagcggctc cggcacagac tactctctga ccatcagcaa cctggagcag 240

gaggatatcg ccacctattt ctgccagcag ggcaatacac tgccctacac ctttggcggc 300

ggcacaaagc tggagatcac cggcggcggc ggctctggag gaggaggcag cggcggagga 360

ggctccgagg tgaagctgca ggagtccgga ccaggcctgg tggcaccatc tcagagcctg 420

tccgtgacat gtaccgtgag cggcgtgtcc ctgcctgact acggcgtgag ctggatcaga 480

cagccaccta ggaagggcct ggagtggctg ggcgtgatct ggggctccga gacaacatac 540

tataactccg ccctgaagtc tcggctgacc atcatcaagg acaactctaa gagccaggtg 600

ttcctgaaga tgaattccct gcagacagac gataccgcca tctactattg cgccaagcac 660

tactattacg gcggctccta tgccatggat tactggggcc agggcacatc tgtgaccgtg 720

tctagc 726

<210> 652
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 652
gacatccaga tgacacagac cacaagctcc ctgagcgcct ccctgggcga cagagtgacc 60

atcagctgcc gggcctccca ggatatctct aagtatctga actggtacca gcagaagcca 120

gatggcacag tgaagctgct gatctatcac accagccgcc tgcactccgg agtgccctct 180

aggttctctg gcagcggctc cggcacagac tacagcctga ccatctccaa cctggagcag 240

gaggatatcg ccacctattt ctgccagcag ggcaatacac tgccatacac ctttggcggc 300

ggcacaaagc tggagatcac cggaggagga ggcagcggag gaggaggctc cggcggcggc 360

ggctctgagg tgaagctgca ggagtccgga ccaggcctgg tggcaccttc tcagagcctg 420

tccgtgacat gtaccgtgtc tggcgtgagc ctgcccgact acggcgtgtc ttggatcaga 480

cagccaccta ggaagggcct ggagtggctg ggcgtgatct ggggcagcga gacaacatac 540

tataattctg ccctgaagag caggctgacc atcatcaagg acaactctaa gagccaggtg 600

ttcctgaaga tgaattccct gcagacagac gataccgcca tctactattg cgccaagcac 660

tactattacg gcggctctta tgccatggat tactggggcc agggcacaag cgtgaccgtg 720

tctagc 726

<210> 653
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 653
gacatccaga tgacacagac cacaagctcc ctgagcgcct ccctgggcga cagagtgacc 60

atctcttgcc gggccagcca ggatatctcc aagtatctga actggtacca gcagaagcca 120

gatggcacag tgaagctgct gatctatcac acctctcgcc tgcacagcgg agtgccctcc 180

aggttctctg gcagcggctc cggcacagac tactctctga ccatcagcaa cctggagcag 240

gaggatatcg ccacctattt ctgccagcag ggcaatacac tgccctacac ctttggcggc 300

ggcacaaagc tggagatcac cggcggcggc ggctctggag gaggaggcag cggcggagga 360

ggctccgagg tgaagctgca ggagtccgga ccaggcctgg tggcaccatc tcagagcctg 420

tccgtgacat gtaccgtgag cggcgtgtcc ctgcctgact acggcgtgag ctggatcaga 480

cagccaccta ggaagggcct ggagtggctg ggcgtgatct ggggctccga gacaacatac 540

tataattccg ccctgaagtc tcggctgaca atcatcaagg acaactctaa gagccaggtg 600

tttctgaaga tgaatagcct gcagacagac gataccgcca tctactattg cgccaagcac 660

tactattacg gcggctccta tgccatggat tactggggcc agggcacatc tgtgaccgtg 720

tctagc 726

<210> 654
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 scFv sequence

<400> 654
gacatccaga tgacacagac cacaagctcc ctgagcgcct ccctgggcga cagagtgacc 60

atcagctgcc gggcctccca ggatatctct aagtatctga actggtacca gcagaagcca 120

gatggcacag tgaagctgct gatctatcac accagccgcc tgcactccgg agtgccctct 180

aggttctctg gcagcggctc cggcacagac tacagcctga ccatctccaa cctggagcag 240

gaggatatcg ccacctattt ctgccagcag ggcaatacac tgccatacac ctttggcggc 300

ggcacaaagc tggagatcac cggaggagga ggcagcggag gaggaggctc cggcggcggc 360

ggctctgagg tgaagctgca ggagtccgga ccaggcctgg tggcaccttc tcagagcctg 420

tccgtgacat gtaccgtgtc tggcgtgagc ctgcccgact acggcgtgtc ttggatcaga 480

cagccaccta ggaagggcct ggagtggctg ggcgtgatct ggggcagcga gacaacatac 540

tataattctg ccctgaagag caggctgaca atcatcaagg acaactctaa gagccaggtg 600

tttctgaaga tgaatagcct gcagacagac gataccgcca tctactattg tgccaagcac 660

tactattacg gcggcagcta tgccatggat tactggggcc agggcacatc cgtgaccgtg 720

tctagc 726

<210> 655
<211> 207
<212> DNA
<213> Homo sapiens

<400> 655
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggcg cagtgcacac gagggggctg 120

gacttcgcct gtgatatcta catctgggcg cccttggccg ggacttgtgg ggtccttctc 180

ctgtcactgg ttatcacttt actgccc 207

<210> 656
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 656
accacaaccc cagcacctcg cccaccaaca ccagcaccaa ccatcgcatc ccagccactg 60

tctctgaggc ccgaggcatg taggcctgca gcaggaggcg ccgtgcacac caggggcctg 120

gactttgcct gcgat 135

<210> 657
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 657
acaacaaccc cagcacccag acctccaaca cctgcaccaa ccatcgcaag ccagcctctg 60

tccctgaggc ccgaggcatg taggccagca gcaggaggcg ccgtgcacac ccggggcctg 120

gactttgcct gcgat 135

<210> 658
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 658
accacaaccc cagcaccccg cccaccaaca cctgcaccaa ccatcgcctc ccagccactg 60

tctctgaggc ccgaggcatg taggcctgca gcaggaggcg ccgtgcacac caggggcctg 120

gactttgcct gcgat 135

<210> 659
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 659
accacaaccc cagcacccag accaccaaca cctgcaccaa ccatcgcaag ccagcctctg 60

tccctgcgcc cagaggcatg caggccagca gcaggaggag cagtgcacac ccggggcctg 120

gacttcgcat gtgat 135

<210> 660
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 660
accacaaccc cagcacctcg cccaccaaca ccagcaccaa ccatcgcatc ccagccactg 60

tctctgcgcc ccgaggcatg caggcctgca gcaggcggcg ccgtgcacac caggggcctg 120

gacttcgcct gtgat 135

<210> 661

<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 661
agggtgaagt tttctaggag cgccgatgca ccagcatata agcagggaca gaaccagctg 60

tacaacgagc tgaatctggg caggagagag gagtacgacg tgctggataa gaggagggga 120

agggaccccg agatgggagg caagccaagg agaaagaacc cccaggaggg cctgtataat 180

gagctgcaga aggacaagat ggccgaggcc tactccgaga tcggcatgaa gggagagcgg 240

cgcaggggca agggacacga tggcctgtat cagggcctgt ctacagccac caaggacacc 300

tacgatgcac tgcacatgca ggccctgcct ccaagg 336

<210> 662
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 662
agggtgaagt tttccaggtc tgccgatgcc cccgcctata agcagggcca gaatcagctg 60

tacaacgagc tgaatctggg caggagagag gagtacgacg tgctggataa gaggagggga 120

cgcgaccccg agatgggagg caagcctagg agaaagaacc cacaggaggg cctgtataat 180

gagctgcaga aggacaagat ggccgaggcc tactctgaga tcggcatgaa gggagagcgg 240

cgcaggggca agggacacga tggcctgtat cagggcctga gcacagccac caaggacacc 300

tacgatgcac tgcacatgca ggccctgcca cctagg 336

<210> 663
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

construct

<400> 663
agggtgaagt ttagcaggtc cgccgatgcc ccagcctata agcagggcca gaaccagctg 60

tacaacgagc tgaatctggg caggagggaa gagtacgacg tgctggataa gaggagagga 120

agggaccccg agatgggagg caagccaagg aggaagaacc cacaggaggg cctgtataat 180

gagctgcaga aggacaagat ggccgaggcc tacagcgaga tcggcatgaa gggagagagg 240

agacggggca agggacacga tggcctgtat cagggcctgt ccacagccac caaggacacc 300

tacgatgcac tgcacatgca ggccctgcct ccaagg 336

<210> 664
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 664
agggtgaagt tttccaggtc tgccgatgcc ccagcctata agcagggcca gaatcagctg 60

tacaacgagc tgaatctggg caggagagag gagtacgacg tgctggataa gaggagggga 120

cgcgaccccg agatgggagg caagcctagg agaaagaacc cacaggaggg cctgtataat 180

gagctgcaga aggacaagat ggccgaggcc tactctgaga tcggcatgaa gggagagcgg 240

cgcaggggca agggacacga tggcctgtat cagggcctga gcacagccac caaggacacc 300

tacgatgcac tgcacatgca ggccctgcca cctagg 336

<210> 665
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 665
agggtgaagt ttagcaggtc cgccgatgcc ccagcctata agcagggcca gaaccagctg 60

tacaacgagc tgaatctggg caggagggaa gagtacgacg tgctggataa gaggagagga 120

agggaccccg agatgggagg caagccaagg aggaagaacc cacaggaggg cctgtataat 180

gagctgcaga aggacaagat ggccgaggcc tactccgaga tcggcatgaa gggagagagg 240

agacggggca agggacacga tggcctgtat cagggcctgt ctacagccac caaggacacc 300

tacgatgcac tgcacatgca ggccctgcct ccaagg 336

<210> 666
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 666
aagagaggcc ggaagaagct gctgtacatc ttcaagcagc ccttcatgag gcccgtgcag 60

acaacccagg aggaggacgg ctgcagctgt cggttcccag aggaggagga gggaggatgt 120

gagctg 126

<210> 667
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 667
aagcgcggca ggaagaagct gctgtacatc ttcaagcagc cctttatgcg ccctgtgcag 60

acaacccagg aggaggacgg ctgcagctgt aggttcccag aggaggagga gggaggatgt 120

gagctg 126

<210> 668
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 668
aagcgcggca ggaagaagct gctgtacatc ttcaagcagc cttttatgcg cccagtgcag 60

acaacccagg aggaggacgg ctgcagctgt aggttccctg aggaggagga gggaggatgt 120

gagctg 126

<210> 669
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 669
aagcgcggca ggaagaagct gctgtacatc ttcaagcagc cctttatgcg ccctgtgcag 60

acaacccagg aggaggacgg ctgcagctgt aggttccctg aggaggagga gggaggatgt 120

gagctg 126

<210> 670
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 670
aagcgcggca ggaagaagct gctgtacatc ttcaagcagc cttttatgcg cccagtgcag 60

acaacccagg aggaggacgg ctgcagctgt aggttccctg aggaggagga gggaggatgc 120

gagctg 126

<210> 671
<211> 63
<212> DNA
<213> Homo sapiens

<400> 671
atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60

ccg 63

<210> 672
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 672
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

ccc 63

<210> 673
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 673
atggcactgc cagtgacagc cctgctgctg cctctggccc tgctgctgca cgcagccaga 60

cct 63

<210> 674
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 674
atggcactgc ctgtgacagc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cct 63

<210> 675
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 675
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cct 63

<210> 676
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 676
ggaggcagcg gagga 15

<210> 677
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 677
ggaggctctg gagga 15

<210> 678
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 678
ggaggctccg gcgga 15

<210> 679
<211> 15
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 679
ggaggatccg gaggc 15

<210> 680
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 680
ggaggatctg gagga 15

<210> 681
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
cleavage site

<400> 681
gagtctaggc gcgtgcggag aaataagcgg agcaag 36

<210> 682
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
cleavage site

<400> 682
gagtctcgga gagtgaggcg caataagagg agcaag 36

<210> 683
<211> 36
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
cleavage site

<400> 683
gagtccagga gagtgcggcg caacaagagg agcaag 36

<210> 684
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 684
ggagtgcagg tggagacaat ctctcctggc gatggccgga ccttcccaaa gagaggccag 60

acatgcgtgg tgcactacac cggcatgctg gaggacggca agaaggtgga cagctcccgg 120

gatagaaaca agccattcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc tgtgggccag agagccaagc tgacaatcag ccctgattac 240

gcatatggag caaccggaca cccaggaatc atcccacctc acgccaccct ggtgtttgat 300

gtggagctgc tgaagccaga g 321

<210> 685
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 685
ggcgtgcagg tggagacaat ctcccctggc gatggccgga ccttcccaaa gagaggccag 60

acatgcgtgg tgcactacac cggcatgctg gaggacggca agaaggtgga cagctcccgg 120

gatagaaaca agcctttcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc tgtgggccag agagccaagc tgacaatcag ccctgattac 240

gcatatggag caaccggaca cccaggaatc atcccacctc acgccaccct ggtgtttgac 300

gtggagctgc tgaagccaga g 321

<210> 686
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 686
ggagtgcagg tggagacaat ctcccctggc gatggcagga ccttcccaaa gcgcggccag 60

acatgcgtgg tgcactacac cggcatgctg gaggacggca agaaggtgga cagctcccgg 120

gatagaaaca agccattcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc cgtgggacag cgcgccaagc tgacaatctc tcctgattac 240

gcatatggag caaccggaca cccaggaatc atcccacctc acgccaccct ggtgtttgac 300

gtggagctgc tgaagcccga g 321

<210> 687
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 687
atctctctga tcgccgccct ggccgtggat tacgtgatcg gcatggagaa cgccatgcca 60

tggaatctgc cagcagacct ggcatggttc aagaggaaca cactgaataa gccagtgatc 120

atgggcagac acacctggga gtccatcggc cggccactgc caggcagaaa gaacatcatc 180

ctgagctccc agcccggcac agacgatagg gtgacctggg tgaagagcgt ggacgaggca 240

atcgcagcat gcggcgatgt gcctgagatc atggtcatcg gaggaggacg cgtgatcgag 300

cagttcctgc caaaggccca gaagctgtac ctgacacaca tcgatgccga ggtggagggc 360

gacacccact ttcctgatta tgagccagac gattgggagt ccgtgttctc tgagtttcac 420

gacgccgatg cccagaactc tcacagctat tgttttgaga tcctggagcg gaga 474

<210> 688
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 688
ggcgtgcagg tggagacaat cagccccggc gatggccgga cctttcctaa gagaggccag 60

acatgcgtgg tgcactacac cggcatgctg ggcgacggca agaaggtgga cagctccagg 120

gatcgcaata agcccttcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc cgtgggacag ggcgccaagc tgacaatctc tccagattac 240

gcatatggag caaccggaca cccaggaatc atcccacccc acgccaccct ggtgttcgac 300

gtggagctgc tggagctgga gtga 324

<210> 689
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 689
ggagtgcagg tggagacaat cagccccggc gatggcagga cctttcctaa gcgcggccag 60

acatgcgtgg tgcactacac cggcatgctg ggcgacggca agaaggtgga cagctcccgg 120

gatagaaata agcccttcaa gtttatgctg ggcaagcagg aagtgatcag aggctgggag 180

gagggagtgg cacagatgtc tgtgggacag ggcgccaagc tgacaatcag cccagattac 240

gcatatggag caaccggaca cccaggaatc atcccacccc acgccaccct ggtgttcgac 300

gtggagctgc tggagctgga gtga 324

<210> 690
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 690
ggcgtgcagg tggagacaat cagccccggc gatggccgga cctttcctaa gcgcggccag 60

acatgcgtgg tgcactacac cggcatgctg ggcgacggca agaaggtgga cagctccagg 120

gatagaaaca agccattcaa gtttatgctg ggcaagcagg aagtgatcag aggatgggag 180

gagggagtgg cacagatgtc cgtgggacag ggcgccaagc tgacaatctc tccagattac 240

gcatatggag caaccggaca cccaggaatc atcccacccc acgccaccct ggtgttcgac 300

gtggagctgc tggagctgga gtga 324

<210> 691
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 691
ggagtgcagg tggagacaat cagcccaggc gacggaagga cattcccaaa gaggggacag 60

acctgcgtgg tgcactacac aggcatgctg ggcgatggca agaaggtgga cagctcccgg 120

gatagaaaca agcccttcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc cgtgggacag ggcgccaagc tgaccatctc tcctgactac 240

gcctatggag caacaggaca cccaggaatc atcccacctc acgccaccct ggtgtttgat 300

gtggagctgc tggagctgga gtga 324

<210> 692
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 692

atctccctga tcgccgccct ggccgtggat tatgtgatcg gcatggagaa cgccatgccc 60

tggaatctgc ccgccgacct ggcctggttc aagaggaata ccctgaacaa gcccgtcatc 120

atgggcaggc acacctggga aagcatcggc agacccctgc ccggcaggaa gaacatcatc 180

ctgtccagcc agcccggcac cgacgacaga gtgacctggg tgaagagcgt ggacgaagct 240

atcgccgctt gcggcgacgt gcccgagatc atggtgatcg gcggcggcag ggtgatcgaa 300

cagttcctgc ccaaggccca gaagctgtac ctgacccaca tcgatgccga ggtggaaggc 360

gatacacact tccccgatta cgaacctgac gactgggaaa gcgtgttttc cgaattccac 420

gacgccgacg cccagaacag ccacagctac tgcttcgaga tcctggaaag aagg 474

<210> 693
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 693
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 694
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 694
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 695
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 695
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aattcatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 696
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 696
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttcagaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaaga accgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagt tcatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgattg a 561

<210> 697
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 697
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttcaagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 698
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 698
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttaagaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaaga accgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagg ccatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgattg a 561

<210> 699
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 699
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttcaagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agttccgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 700
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 700
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttttcaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaagt tccgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagg ccatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgattg a 561

<210> 701
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 701
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaaggtg a 1461

<210> 702
<211> 1782
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 702
atggcactgc cagtgacagc cctgctgctg cctctggccc tgctgctgca cgcagccaga 60

cctgacatcc agatgacaca gaccacaagc tccctgagcg cctccctggg cgacagagtg 120

accatctctt gccgggccag ccaggatatc tccaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacacctctc gcctgcacag cggcgtgcct 240

tccaggttct ctggcagcgg ctccggcaca gactactctc tgaccatcag caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcccta cacctttggc 360

ggcggcacaa agctggagat caccggcggc ggcggctctg gaggaggagg cagcggcgga 420

ggaggctccg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc atctcagagc 480

ctgtccgtga catgtaccgt gagcggcgtg tccctgcctg actacggcgt gagctggatc 540

agacagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggctc cgagacaaca 600

tactataact ccgccctgaa gtctcggctg accatcatca aggacaactc taagagccag 660

gtgttcctga agatgaattc cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggctc ctatgccatg gattactggg gccagggcac atctgtgacc 780

gtgtctagcg gcgtgcaggt ggagacaatc agcccaggcg acggacgcac ctttccaaag 840

aggggacaga catgcgtggt gcactacacc ggcatgctgg aggatggcaa gaaggtggac 900

tcctctagag atcggaataa gccattcaag tttatgctgg gcaagcagga agtgatcaga 960

ggctgggagg agggagtggc acagatgtct gtgggacagc gggccaagct gacaatcagc 1020

cctgactatg catacggagc aaccggacac ccaggaatca tcccaccaca cgccacactg 1080

gtgttcgatg tggagctgct gaagcctgag acaacaaccc cagcacccag acctccaaca 1140

cctgcaccaa ccatcgcaag ccagcctctg tccctgaggc ccgaggcatg taggccagca 1200

gcaggaggcg ccgtgcacac ccggggcctg gactttgcct gcgatatcta tatctgggca 1260

ccactggcag gaacatgtgg cgtgctgctg ctgtccctgg tcatcaccct gtattgcaag 1320

cgcggcagga agaagctgct gtacatcttc aagcagccct ttatgcgccc tgtgcagaca 1380

acccaggagg aggacggctg cagctgtagg ttcccagagg aggaggaggg aggatgtgag 1440

ctgagggtga agttttccag gtctgccgat gcccccgcct ataagcaggg ccagaatcag 1500

ctgtacaacg agctgaatct gggcaggaga gaggagtacg acgtgctgga taagaggagg 1560

ggacgcgacc ccgagatggg aggcaagcct aggagaaaga acccacagga gggcctgtat 1620

aatgagctgc agaaggacaa gatggccgag gcctactctg agatcggcat gaagggagag 1680

cggcgcaggg gcaagggaca cgatggcctg tatcagggcc tgagcacagc caccaaggac 1740

acctacgatg cactgcacat gcaggccctg ccacctaggt ga 1782

<210> 703
<211> 1935
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 703
atggcactgc ctgtgacagc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cctgacatcc agatgacaca gaccacaagc tccctgagcg cctccctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

ccagatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgccc 240

tctaggttct ctggcagcgg ctccggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgccata cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc ttctcagagc 480

ctgtccgtga catgtaccgt gtctggcgtg agcctgcccg actacggcgt gtcttggatc 540

agacagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcaggctg accatcatca aggacaactc taagagccag 660

gtgttcctga agatgaattc cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggctc ttatgccatg gattactggg gccagggcac aagcgtgacc 780

gtgtctagca tctccctgat cgccgccctg gcagtggact acgtgatcgg catggagaac 840

gccatgccct ggaatctgcc tgccgatctg gcctggttta agagaaacac actgaataag 900

cccgtgatca tgggccggca cacctgggag tctatcggca ggcccctgcc tggcaggaag 960

aacatcatcc tgtcctctca gcctggcaca gacgatagag tgacctgggt gaagagcgtg 1020

gacgaggcaa tcgcagcatg tggcgatgtg cccgagatca tggtcatcgg cggcggcaga 1080

gtgatcgagc agttcctgcc taaggcccag aagctgtatc tgacacacat cgacgccgag 1140

gtggagggcg acacccactt tccagattac gagcccgacg attgggagtc cgtgttctct 1200

gagtttcacg acgccgatgc ccagaattcc cactcttatt gcttcgagat cctggagagg 1260

agaaccacaa ccccagcacc ccgcccacca acacctgcac caaccatcgc ctcccagcca 1320

ctgtctctga ggcccgaggc atgtaggcct gcagcaggag gcgccgtgca caccaggggc 1380

ctggactttg cctgcgatat ctacatctgg gcacctctgg caggaacatg tggcgtgctg 1440

ctgctgtccc tggtcatcac cctgtattgc aagcgcggca ggaagaagct gctgtacatc 1500

ttcaagcagc cttttatgcg cccagtgcag acaacccagg aggaggacgg ctgcagctgt 1560

aggttccctg aggaggagga gggaggatgt gagctgaggg tgaagtttag caggtccgcc 1620

gatgccccag cctataagca gggccagaac cagctgtaca acgagctgaa tctgggcagg 1680

agggaagagt acgacgtgct ggataagagg agaggaaggg accccgagat gggaggcaag 1740

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gaggcctaca gcgagatcgg catgaaggga gagaggagac ggggcaaggg acacgatggc 1860

ctgtatcagg gcctgtccac agccaccaag gacacctacg atgcactgca catgcaggcc 1920

ctgcctccaa ggtga 1935

<210> 704
<211> 1782
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 704
atggcactgc cagtgacagc cctgctgctg cctctggccc tgctgctgca cgcagccaga 60

cctgacatcc agatgacaca gaccacaagc tccctgagcg cctccctggg cgacagagtg 120

accatctctt gccgggccag ccaggatatc tccaagtatc tgaactggta ccagcagaag 180

ccagatggca cagtgaagct gctgatctat cacacctctc gcctgcacag cggagtgccc 240

tccaggttct ctggcagcgg ctccggcaca gactactctc tgaccatcag caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcccta cacctttggc 360

ggcggcacaa agctggagat caccggcggc ggcggctctg gaggaggagg cagcggcgga 420

ggaggctccg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc atctcagagc 480

ctgtccgtga catgtaccgt gagcggcgtg tccctgcctg actacggcgt gagctggatc 540

agacagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggctc cgagacaaca 600

tactataatt ccgccctgaa gtctcggctg acaatcatca aggacaactc taagagccag 660

gtgtttctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggctc ctatgccatg gattactggg gccagggcac atctgtgacc 780

gtgtctagca ccacaacccc agcacccaga ccaccaacac ctgcaccaac catcgcaagc 840

cagcctctgt ccctgcgccc agaggcatgc aggccagcag caggaggagc agtgcacacc 900

cggggcctgg acttcgcatg tgatggagtg caggtggaga caatctcccc aggcgacggc 960

agaacctttc ccaagcgggg ccagacatgc gtggtgcact ataccggcat gctggaggat 1020

ggcaagaagg tggactcctc tagagatcgg aacaagccat tcaagtttat gctgggcaag 1080

caggaagtga tcagaggctg ggaggaggga gtggcacaga tgtctgtggg acagcgggcc 1140

aagctgacaa tcagcccaga ctatgcatac ggagcaaccg gacaccctgg aatcatccct 1200

ccacacgcca ccctggtgtt cgatgtggag ctgctgaagc ctgagatcta catctgggca 1260

ccactggcag gaacatgcgg cgtgctgctg ctgtccctgg tcatcaccct gtattgtaag 1320

cgcggcagga agaagctgct gtacatcttc aagcagccct ttatgcgccc tgtgcagaca 1380

acccaggagg aggacggctg cagctgtagg ttccctgagg aggaggaggg aggatgtgag 1440

ctgagggtga agttttccag gtctgccgat gccccagcct ataagcaggg ccagaatcag 1500

ctgtacaacg agctgaatct gggcaggaga gaggagtacg acgtgctgga taagaggagg 1560

ggacgcgacc ccgagatggg aggcaagcct aggagaaaga acccacagga gggcctgtat 1620

aatgagctgc agaaggacaa gatggccgag gcctactctg agatcggcat gaagggagag 1680

cggcgcaggg gcaagggaca cgatggcctg tatcagggcc tgagcacagc caccaaggac 1740

acctacgatg cactgcacat gcaggccctg ccacctaggt ga 1782

<210> 705
<211> 1935
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 705
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cctgacatcc agatgacaca gaccacaagc tccctgagcg cctccctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

ccagatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgccc 240

tctaggttct ctggcagcgg ctccggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgccata cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc ttctcagagc 480

ctgtccgtga catgtaccgt gtctggcgtg agcctgcccg actacggcgt gtcttggatc 540

agacagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcaggctg acaatcatca aggacaactc taagagccag 660

gtgtttctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgtgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

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atcggcatgg agaacgccat gccctggaat ctgcctgccg atctggcctg gtttaagaga 1020

aacacactga ataagcccgt gatcatgggc cggcacacct gggagagcat cggcagacct 1080

ctgccaggcc ggaagaacat catcctgtcc tctcagcctg gcacagacga tagagtgacc 1140

tgggtgaagt ccgtggacga ggcaatcgca gcatgcggcg atgtgcccga gatcatggtc 1200

atcggcggcg gcagagtgat cgagcagttc ctgcctaagg cccagaagct gtatctgaca 1260

cacatcgacg ccgaggtgga gggcgacacc cactttccag attacgagcc cgacgattgg 1320

gagtccgtgt tctctgagtt tcacgacgcc gatgcccaga attcccactc ttattgtttc 1380

gagatcctgg agagaagaat ctacatctgg gcacctctgg caggaacatg cggcgtgctg 1440

ctgctgtctc tggtcatcac cctgtattgt aagcgcggca ggaagaagct gctgtacatc 1500

ttcaagcagc cttttatgcg cccagtgcag acaacccagg aggaggacgg ctgcagctgt 1560

aggttccctg aggaggagga gggaggatgc gagctgaggg tgaagtttag caggtccgcc 1620

gatgccccag cctataagca gggccagaac cagctgtaca acgagctgaa tctgggcagg 1680

agggaagagt acgacgtgct ggataagagg agaggaaggg accccgagat gggaggcaag 1740

ccaaggagga agaacccaca ggagggcctg tataatgagc tgcagaagga caagatggcc 1800

gaggcctact ccgagatcgg catgaaggga gagaggagac ggggcaaggg acacgatggc 1860

ctgtatcagg gcctgtctac agccaccaag gacacctacg atgcactgca catgcaggcc 1920

ctgcctccaa ggtga 1935

<210> 706
<211> 1950

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 706
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggaatctccc tgatcgccgc cctggcagtg 1500

gaccacgtga tcggcatgga gaacgccatg ccatggaatc tgcccgccga tctggcctgg 1560

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ggcaggcccc tgcctggacg caagaacatc atcctgagct cccagcccgg caccgacgat 1680

agggtgacat gggtgaagtc cgtggacgag gcaatcgcag catgcggcga tgtgcccgag 1740

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tatctgaccc acatcgacgc cgaggtggag ggcgacacac actttcctga ttacaagcca 1860

gacgattggg agtccgtgtt ctctgagttt cacgacgccg atgcccagaa ttctcacagc 1920

tattgttttg agatcctgga gcggagatga 1950

<210> 707
<211> 1797
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 707
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

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ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

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cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

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agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggctctgga ggaggagtgc aggtggagac aatcagccca 1500

ggcgacggaa ggacattccc aaagagggga cagacctgcg tggtgcacta cacaggcatg 1560

ctgggcgatg gcaagaaggt ggacagctcc cgggatagaa acaagccctt caagtttatg 1620

ctgggcaagc aggaagtgat caggggatgg gaggagggag tggcacagat gtccgtggga 1680

cagggcgcca agctgaccat ctctcctgac tacgcctatg gagcaacagg acacccagga 1740

atcatcccac ctcacgccac cctggtgttt gatgtggagc tgctggagct ggagtga 1797

<210> 708
<211> 2034
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 708

atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

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tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

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cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggagtgggct ccctgaactg catcgtggcc 1500

gtgagccaga acatgggcat cggcaagaat ggcgacctgc cttggccacc tctgaggaac 1560

gagttcagat actttcagag gatgaccaca accagctccg tggagggcaa gcagaacctg 1620

gtcatcatgg gcaagaagac atggttctct atccccgaga agaaccgccc tctgaagggc 1680

cggatcaatc tggtgctgag cagagagctg aaggagccac cacagggagc acacttcctg 1740

agccggagcc tggacgatgc cctgaagctg accgagcagc ccgagctggc caacaaggtg 1800

gacatggtgt ggatcgtggg cggctctagc gtgatcaagg aggccatgaa tcacccaggc 1860

cacctgaagc tgttcgtgac aagaatcatg caggactttg agtccgatac cttctttccc 1920

gagatcgacc tggagaagta caagctgctg cctgagtatc caggcgtgct gtctgatgtg 1980

caggaggaga agggcatcaa gtacaagttc gaggtgtatg agaagaatga ttga 2034

<210> 709
<211> 2034
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 709
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

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caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

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gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggagtgggct ccctgaactg catcgtggcc 1500

gtgagccaga acatgggcat cggcaagaat ggcgacctgc cttggccacc tctgaggaac 1560

gagttcagat actttcagag gatgaccaca accagctccg tggagggcaa gcagaacctg 1620

gtcatcatgg gcaagaagac atggttctct atccccgaga agaaccgccc tctgaagggc 1680

cggatcaatc tggtgctgag cagagagctg aaggagccac cacagggagc acacttcctg 1740

agccggagcc tggacgatgc cctgaagctg accgagcagc ccgagctggc caacaaggtg 1800

gacatggtgt ggatcgtggg cggctctagc gtgatcaagg agttcatgaa tcacccaggc 1860

cacctgaagc tgttcgtgac aagaatcatg caggactttg agtccgatac cttctttccc 1920

gagatcgacc tggagaagta caagctgctg cctgagtatc caggcgtgct gtctgatgtg 1980

caggaggaga agggcatcaa gtacaagttc gaggtgtatg agaagaatga ttga 2034

<210> 710
<211> 2034
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 710
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

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tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

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ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggagtgggct ccctgaactg catcgtggcc 1500

gtgagccaga acatgggcat cggcaagaat ggcgacctgc cttggccacc tctgaggaac 1560

gagttcagat actttaagag gatgaccaca accagctccg tggagggcaa gcagaacctg 1620

gtcatcatgg gcaagaagac atggttctct atccccgaga agaaccgccc tctgaagggc 1680

cggatcaatc tggtgctgag cagagagctg aaggagccac cacagggagc acacttcctg 1740

agccggagcc tggacgatgc cctgaagctg accgagcagc ccgagctggc caacaaggtg 1800

gacatggtgt ggatcgtggg cggctctagc gtgatcaagg aggccatgaa tcacccaggc 1860

cacctgaagc tgttcgtgac aagaatcatg caggactttg agtccgatac cttctttccc 1920

gagatcgacc tggagaagta caagctgctg cctgagtatc caggcgtgct gtctgatgtg 1980

caggaggaga agggcatcaa gtacaagttc gaggtgtatg agaagaatga ttga 2034

<210> 711
<211> 2034
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 711
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cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

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aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggagtgggct ccctgaactg catcgtggcc 1500

gtgagccaga acatgggcat cggcaagaat ggcgacctgc cttggccacc tctgaggaac 1560

gagttcagat acttttcag gatgaccaca accagctccg tggagggcaa gcagaacctg 1620

gtcatcatgg gcaagaagac atggttctct atccccgaga agttccgccc tctgaagggc 1680

cggatcaatc tggtgctgag cagagagctg aaggagccac cacagggagc acacttcctg 1740

agccggagcc tggacgatgc cctgaagctg accgagcagc ccgagctggc caacaaggtg 1800

gacatggtgt ggatcgtggg cggctctagc gtgatcaagg aggccatgaa tcacccaggc 1860

cacctgaagc tgttcgtgac aagaatcatg caggactttg agtccgatac cttctttccc 1920

gagatcgacc tggagaagta caagctgctg cctgagtatc caggcgtgct gtctgatgtg 1980

caggaggaga agggcatcaa gtacaagttc gaggtgtatg agaagaatga ttga 2034

<210> 712
<211> 1824
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic construct

<400> 712
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

ccttctggag gcgtgcaggt ggagacaatc agcccaggcg acggacgcac cttcccaaag 120

aggggacaga catgcgtggt gcactacacc ggcatgctgg aggatggcaa gaaggtggac 180

agctccagag atcggaacaa gccattcaag tttatgctgg gcaagcagga agtgatcaga 240

ggatgggagg agggagtggc acagatgagc gtgggacagc gggccaagct gacaatctcc 300

cctgactatg catacggagc aaccggacac ccaggaatca tcccacctca cgccacactg 360

gtgttcgacg tggagctgct gaagcctgag gagtccagga gagtgcggcg caacaagcgg 420

tctaaggata tccagatgac acagaccaca agctccctgt ccgcctctct gggcgacaga 480

gtgaccatca gctgccgggc ctcccaggat atctctaagt atctgaactg gtaccagcag 540

aagcccgatg gcacagtgaa gctgctgatc tatcacacca gccgcctgca ctccggagtg 600

ccttctaggt tcagcggctc cggctctggc acagactaca gcctgaccat ctccaacctg 660

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atcaggcagc cacctaggaa gggcctggag tggctgggcg tgatctgggg cagcgagaca 960

acatactata attctgccct gaagagcaga ctgacaatca tcaaggacaa cagcaagtcc 1020

caggtgttcc tgaagatgaa tagcctgcag acagacgata ccgccatcta ctattgcgcc 1080

aagcactact attacggcgg cagctatgcc atggattact ggggccaggg cacatccgtg 1140

accgtgtcta gcaccacaac cccagcacct cgcccaccaa caccagcacc aaccatcgca 1200

tcccagccac tgtctctgag gcccgaggca tgtaggcctg cagcaggagg cgccgtgcac 1260

accaggggcc tggactttgc ctgcgatatc tatatctggg caccactggc aggaacatgt 1320

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ctgggcagga gagaggagta cgacgtgctg gataagagga ggggaaggga ccccgagatg 1620

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aagatggccg aggcctactc cgagatcggc atgaagggag agcggcgcag gggcaaggga 1740

cacgatggcc tgtatcaggg cctgtctaca gccaccaagg acacctacga tgcactgcac 1800

atgcaggccc tgcctccaag gtga 1824

<210> 713
<211> 1977
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 713
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

ccttctggaa tcagcctgat cgccgccctg gcagtggact acgtgatcgg catggagaac 120

gccatgccct ggaatctgcc tgccgatctg gcctggttca agagaaacac actgaataag 180

cccgtgatca tgggccggca cacctgggag tccatcggca ggcccctgcc tggcaggaag 240

aacatcatcc tgagctccca gcctggcaca gacgatagag tgacctgggt gaagagcgtg 300

gacgaggcaa tcgcagcatg cggcgatgtg cccgagatca tggtcatcgg cggcggcaga 360

gtgatcgagc agttcctgcc taaggcccag aagctgtatc tgacacacat cgacgccgag 420

gtggagggcg acacccactt tccagattac gagcccgacg attgggagtc cgtgttctct 480

gagtttcacg acgccgatgc ccagaacagc cactcctact gcttcgagat cctggagagg 540

agagagtctc ggcgcgtgag gagaaataag agaagcaagg acatccagat gacacagacc 600

acaagctccc tgtccgcctc tctgggcgac agagtgacca tcagctgccg ggcctcccag 660

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cagacagacg ataccgccat ctactattgc gccaagcact actattacgg cggcagctat 1260

gccatggatt actggggcca gggcacatcc gtgaccgtgt ctagcaccac aaccccagca 1320

cctcgcccac caacaccagc accaaccatc gcatcccagc cactgtctct gaggcccgag 1380

gcatgtaggc ctgcagcagg aggcgccgtg cacaccaggg gcctggactt tgcctgcgat 1440

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gagggaggat gtgagctgag ggtgaagttt tctaggagcg ccgatgcacc agcatataag 1680

cagggacaga accagctgta caacgagctg aatctgggca ggagagagga gtacgacgtg 1740

ctggataaga ggaggggaag ggaccccgag atgggaggca agccaaggag aaagaacccc 1800

caggagggcc tgtataatga gctgcagaag gacaagatgg ccgaggccta ctccgagatc 1860

ggcatgaagg gagagcggcg caggggcaag ggacacgatg gcctgtatca gggcctgtct 1920

acagccacca aggacaccta cgatgcactg cacatgcagg ccctgcctcc aaggtga 1977

<210> 714
<211> 2061
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 714
atggcactgc cagtgaccgc cctgctgctg cctctggccc tgctgctgca cgcagccaga 60

ccaagcggag tgggctccct gaactgcatc gtggccgtga gccagaacat gggcatcggc 120

aagaatggcg acctgccatg gccacctctg aggaacgagt tcaggtactt tcagagaatg 180

accacaacca gctccgtgga gggcaagcag aacctggtca tcatgggcaa gaagacctgg 240

ttcagcatcc ccgagaagaa caggcctctg aagggcagaa tcaatctggt gctgtccagg 300

gagctgaagg agccaccaca gggagcccac tttctgtctc gcagcctgga cgatgccctg 360

aagctgacag agcagcccga gctggccaac aaggtggata tggtgtggat cgtgggcggc 420

tctagcgtga tcaaggagtt catgaatcac cccggccacc tgaagctgtt cgtgaccagg 480

atcatgcagg actttgagtc cgatacattc tttcctgaga tcgacctgga gaagtataag 540

ctgctgccag agtaccccgg cgtgctgagc gatgtgcagg aggagaaggg catcaagtat 600

aagtttgagg tgtacgagaa gaacgacgag tctaggagag tgcggcgcaa taagagaagc 660

aaggacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 720

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ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 1140

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tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 1260

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 1320

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cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 1500

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 1560

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1620

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1680

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agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1800

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1860

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1920

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1980

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 2040

caggccctgc ctccaaggtg a 2061

<210> 715
<211> 2061
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 715
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ccaagcggag tgggctccct gaactgcatc gtggccgtga gccagaacat gggcatcggc 120

aagaatggcg acctgccatg gccacctctg aggaacgagt tcaggtactt taagagaatg 180

accacaacca gctccgtgga gggcaagcag aacctggtca tcatgggcaa gaagacctgg 240

ttcagcatcc ccgagaagaa caggcctctg aagggcagaa tcaatctggt gctgtccagg 300

gagctgaagg agccaccaca gggagcccac tttctgtctc gcagcctgga cgatgccctg 360

aagctgacag agcagcccga gctggccaac aaggtggata tggtgtggat cgtgggcggc 420

tctagcgtga tcaaggaggc catgaatcac cccggccacc tgaagctgtt cgtgaccagg 480

atcatgcagg actttgagtc cgatacattc tttcctgaga tcgacctgga gaagtataag 540

ctgctgccag agtaccccgg cgtgctgagc gatgtgcagg aggagaaggg catcaagtat 600

aagttcgagg tgtacgagaa gaacgacgag tctaggagag tgcggcgcaa taagagaagc 660

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ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 1140

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gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 1440

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 1500

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 1560

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1620

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1680

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1740

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1800

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1860

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1920

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1980

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 2040

caggccctgc ctccaaggtg a 2061

<210> 716
<211> 603
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
promoter

<400> 716
aagcttggga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 60

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagggа 120

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 180

aagtgtatca tatgccaagt acgccccctа ttgacgtcaa tgacggtaaa tggcccgcct 240

ggcattatgc ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat 300

tagtcatcgc tattaccatg gtgatgcggt tttggcagta catcaatggg cgtggatagc 360

ggtttgactc acggggattt ccaagtctcc accccattga cgtcaatggg agtttgtttt 420

ggcaccaaaa tcaacgggac tttccaaaat gtcgtaacaa ctccgcccca ttgacgcaaa 480

tgggcggtag gcgtgtacgg tgggaggtct atataagcag agctcgttta gtgaaccgtc 540

agatcgcctg gagacgccat ccacgctgtt ttgacctcca tagaagacac cgactctact 600

aga 603

<210> 717
<211> 1339
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
promoter

<400> 717
cgatagtaat tcatacaaaa ggactcgccc ctgccttggg gaatcccagg gaccgtcgtt 60

aaactcccac taacgtagaa cccagagatc gctgcgttcc cgccccctca cccgcccgct 120

ctcgtcatca ctgaggtgga gaagagcatg cgtgaggctc cggtgcccgt cagtgggcag 180

agcgcacatc gcccacagtc cccgagaagt tgggggggagg ggtcggcaat tgaaccggtg 240

cctagagaag gtggcgcggg gtaaactggg aaagtgatgt cgtgtactgg ctccgccttt 300

ttcccgaggg tgggggagaa ccgtatataa gtgcagtagt cgccgtgaac gttcttttтc 360

gcaacgggtt tgccgccaga acacaggtaa gtgccgtgtg tggttcccgc gggcctggcc 420

tctttacggg ttatggccct tgcgtgcctt gaattacttc cacgcccctg gctgcagtac 480

gtgattcttg atcccgagct tcgggttgga agtgggtggg agagttcgag gccttgcgct 540

taaggagccc cttcgcctcg tgcttgagtt gaggcctggc ttgggcgctg gggccgccgc 600

gtgcgaatct ggtggcacct tcgcgcctgt ctcgctgctt tcgataagtc tctagccatt 660

taaaattttt gatgacctgc tgcgacgctt tttttctggc aagatagtct tgtaaatgcg 720

ggccaagatc tgcacactgg tatttcggtt tttggggccg cgggcggcga cggggcccgt 780

gcgtcccagc gcacatgttc ggcgaggcgg ggcctgcgag cgcggccacc gagaatcgga 840

cgggggtagt ctcaagctgg ccggcctgct ctggtgcctg gcctcgcgcc gccgtgtatc 900

gccccgccct gggcggcaag gctggcccgg tcggcaccag ttgcgtgagc ggaaagatgg 960

ccgcttcccg gccctgctgc agggagctca aaatggagga cgcggcgctc gggagagcgg 1020

gcgggtgagt cacccacaca aaggaaaagg gcctttccgt cctcagccgt cgcttcatgt 1080

gactccacgg agtaccgggc gccgtccagg cacctcgatt agttctcgag cttttggagt 1140

acgtcgtctt taggttgggg ggaggggttt tatgcgatgg agtttcccca cactgagtgg 1200

gtggagactg aagttaggcc agcttggcac ttgatgtaat tctccttgga atttgccctt 1260

tttgagtttg gatcttggtt cattctcaag cctcagacag tggttcaaag ttttttttctt 1320

ccatttcagg tgtcgtgag 1339

<210> 718
<211> 399
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
promoter

<400> 718
ccggtaggcg ccaaccggct ccgttctttg gtggcccctt cgcgccacct tctactcctc 60

ccctagtcag gaagttcccc cccgccccgc agctcgcgtc gtgcaggacg tgacaaatgg 120

aagtagcacg tctcactagt ctcgtgcaga tggacagcac cgctgagcaa tggaagcggg 180

taggcctttg gggcagcggc caatagcagc tttgctcctt cgctttctgg gctcagaggc 240

tgggaagggg tgggtccggg ggcgggctca ggggcgggct caggggcggg gcgggcgccc 300

gaaggtcctc cggaggcccg gcattctgca cgcttcaaaa gcgcacgtct gccgcgctgt 360

tctcctcttc ctcatctccg ggcctttcga cctgcagcc 399

<210> 719
<211> 22
<212> PRT
<213> Homo sapiens

<400> 719
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala
20

<210> 720
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 720
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 721
<211> 9
<212> PRT
<213> Homo sapiens

<400> 721
Ser Ala Arg Asn Arg Gln Lys Arg Ser
1 5

<210> 722
<211> 8
<212> PRT
<213> Homo sapiens

<400> 722
Ala Arg Asn Arg Gln Lys Arg Ser
1 5

<210> 723
<211> 306
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 723
Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
1 5 10 15

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
20 25 30

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
35 40 45

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
50 55 60

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
65 70 75 80

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
85 90 95

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
100 105 110

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
115 120 125

Asp Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln
130 135 140

Gly Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
145 150 155 160

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala

165 170 175

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
180 185 190

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
195 200 205

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
210 215 220

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
225 230 235 240

Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln
245 250 255

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
260 265 270

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
275 280 285

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
290 295 300

Cys Ser
305

<210> 724
<211> 197
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 724
Arg Asn Leu Pro Val Ala Thr Pro Asp Pro Gly Met Phe Pro Cys Leu
1 5 10 15

```
His His Ser Gln Asn Leu Leu Arg Ala Val Ser Asn Met Leu Gln Lys
            20                  25                  30

Ala Arg Gln Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile Asp
        35                  40                  45

His Glu Asp Ile Thr Lys Asp Lys Thr Ser Thr Val Glu Ala Cys Leu
    50                  55                  60

Pro Leu Glu Leu Thr Lys Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr
65                  70                  75                  80

Ser Phe Ile Thr Asn Gly Ser Cys Leu Ala Ser Arg Lys Thr Ser Phe
                85                  90                  95

Met Met Ala Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met Tyr
            100                 105                 110

Gln Val Glu Phe Lys Thr Met Asn Ala Lys Leu Leu Met Asp Pro Lys
        115                 120                 125

Arg Gln Ile Phe Leu Asp Gln Asn Met Leu Ala Val Ile Asp Glu Leu
    130                 135                 140

Met Gln Ala Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser Ser
145                 150                 155                 160

Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu
                165                 170                 175

Leu His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met Ser
            180                 185                 190

Tyr Leu Asn Ala Ser
        195
```

<210> 725
<211> 389
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 725
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln
130 135 140

Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Leu Ser Lys Gly Glu Glu
145 150 155 160

Asp Asn Met Ala Ile Ile Lys Glu Phe Met Arg Phe Lys Val His Met
165 170 175

Glu Gly Ser Val Asn Gly His Glu Phe Glu Ile Glu Gly Glu Gly Glu

180 185 190

Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala Lys Leu Lys Val Thr Lys
195 200 205

Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile Leu Ser Pro Gln Phe Met
210 215 220

Tyr Gly Ser Lys Ala Tyr Val Lys His Pro Ala Asp Ile Pro Asp Tyr
225 230 235 240

Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys Trp Glu Arg Val Met Asn
245 250 255

Phe Glu Asp Gly Gly Val Val Thr Val Thr Gln Asp Ser Ser Leu Gln
260 265 270

Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu Arg Gly Thr Asn Phe Pro
275 280 285

Ser Asp Gly Pro Val Met Gln Lys Lys Thr Met Gly Trp Glu Ala Ser
290 295 300

Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala Leu Lys Gly Glu Ile Lys
305 310 315 320

Gln Arg Leu Lys Leu Lys Asp Gly Gly His Tyr Asp Ala Glu Val Lys
325 330 335

Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln Leu Pro Gly Ala Tyr Asn
340 345 350

Val Asn Ile Lys Leu Asp Ile Thr Ser His Asn Glu Asp Tyr Thr Ile
355 360 365

Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg His Ser Thr Gly Gly Met
370 375 380

Asp Glu Leu Tyr Lys

385

<210> 726
<211> 577
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 726
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Gly Ser Val Gly Ser Leu Asn Cys Ile Val Ala Val
130 135 140

Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro
145 150 155 160

```
Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser
                165                 170                 175

Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe
            180                 185                 190

Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val
        195                 200                 205

Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser
    210                 215                 220

Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala
225                 230                 235                 240

Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys
                245                 250                 255

Glu Ala Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile
            260                 265                 270

Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu
        275                 280                 285

Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln
    290                 295                 300

Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
305                 310                 315                 320

Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
                325                 330                 335

Glu Glu Asn Pro Gly Pro Leu Ser Lys Gly Glu Glu Asp Asn Met Ala
            340                 345                 350

Ile Ile Lys Glu Phe Met Arg Phe Lys Val His Met Glu Gly Ser Val
        355                 360                 365
```

```
Asn Gly His Glu Phe Glu Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr
    370                 375                 380

Glu Gly Thr Gln Thr Ala Lys Leu Lys Val Thr Lys Gly Gly Pro Leu
385                 390                 395                 400

Pro Phe Ala Trp Asp Ile Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys
                405                 410                 415

Ala Tyr Val Lys His Pro Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser
            420                 425                 430

Phe Pro Glu Gly Phe Lys Trp Glu Arg Val Met Asn Phe Glu Asp Gly
        435                 440                 445

Gly Val Val Thr Val Thr Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe
    450                 455                 460

Ile Tyr Lys Val Lys Leu Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro
465                 470                 475                 480

Val Met Gln Lys Lys Thr Met Gly Trp Glu Ala Ser Ser Glu Arg Met
                485                 490                 495

Tyr Pro Glu Asp Gly Ala Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys
            500                 505                 510

Leu Lys Asp Gly Gly His Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys
        515                 520                 525

Ala Lys Lys Pro Val Gln Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys
    530                 535                 540

Leu Asp Ile Thr Ser His Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr
545                 550                 555                 560

Glu Arg Ala Glu Gly Arg His Ser Thr Gly Gly Met Asp Glu Leu Tyr
                565                 570                 575
```

Lys

<210> 727
<211> 652
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 727
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Pro
115 120 125

Glu Gly Gly Ser Gly Gly Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
130 135 140

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu

```
145                 150                 155                 160

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
                165                 170                 175

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
            180                 185                 190

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
        195                 200                 205

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
    210                 215                 220

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
225                 230                 235                 240

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
                245                 250                 255

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
            260                 265                 270

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
        275                 280                 285

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
    290                 295                 300

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
305                 310                 315                 320

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
                325                 330                 335

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
            340                 345                 350

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
```

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        355                 360                 365

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
    370                 375                 380

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
385                 390                 395                 400

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
                405                 410                 415

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
            420                 425                 430

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
        435                 440                 445

Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro Asp
    450                 455                 460

Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala
465                 470                 475                 480

Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro
                485                 490                 495

Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr
            500                 505                 510

Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser
        515                 520                 525

Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu
    530                 535                 540

Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile
545                 550                 555                 560

Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala
```

565 570 575

Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met
580 585 590

Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu
595 600 605

Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr
610 615 620

Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val
625 630 635 640

Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
645 650

<210> 728
<211> 653
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 728
Met Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe
1 5 10 15

Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu
20 25 30

Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys
35 40 45

Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val
50 55 60

Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp
65 70 75 80

```
Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala
                85                  90                  95

Thr Leu Val Phe Asp Val Glu Leu Leu Lys Pro Glu Gly Gly Ser Gly
            100                 105                 110

Gly Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe
        115                 120                 125

Leu Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr
    130                 135                 140

Val Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val
145                 150                 155                 160

Leu Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp
                165                 170                 175

Gln Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val
            180                 185                 190

Lys Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu
        195                 200                 205

Val Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile
    210                 215                 220

Trp Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr
225                 230                 235                 240

Phe Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp
                245                 250                 255

Trp Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser
            260                 265                 270

Arg Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu
        275                 280                 285
```

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Ser Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val
    290                 295                 300

Glu Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro
305                 310                 315                 320

Ile Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr
                325                 330                 335

Thr Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys
            340                 345                 350

Asn Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser
        355                 360                 365

Trp Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu
    370                 375                 380

Thr Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp
385                 390                 395                 400

Arg Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn
                405                 410                 415

Ala Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp
            420                 425                 430

Ser Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly
        435                 440                 445

Gly Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro
    450                 455                 460

Asp Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg
465                 470                 475                 480

Ala Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
                485                 490                 495
```

Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys
500 505 510

Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu
515 520 525

Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys
530 535 540

Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser
545 550 555 560

Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn
565 570 575

Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn
580 585 590

Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser
595 600 605

Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys
610 615 620

Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala
625 630 635 640

Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
645 650

<210> 729
<211> 656
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 729
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu

```
1               5                   10                  15

Ala Ser Pro Leu Val Ala Gly Val Gln Val Glu Thr Ile Ser Pro Gly
            20                  25                  30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
        35                  40                  45

Thr Gly Met Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg
    50                  55                  60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65                  70                  75                  80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
                85                  90                  95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
            100                 105                 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Pro
        115                 120                 125

Glu Ser Ala Arg Asn Arg Gln Lys Arg Ser Ile Trp Glu Leu Lys Lys
    130                 135                 140

Asp Val Tyr Val Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu
145                 150                 155                 160

Met Val Val Leu Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp
                165                 170                 175

Thr Leu Asp Gln Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr
            180                 185                 190

Ile Gln Val Lys Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys
        195                 200                 205

Gly Gly Glu Val Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu
```

210 215 220

Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys
225 230 235 240

Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe
245 250 255

Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val
260 265 270

Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala
275 280 285

Ala Thr Leu Ser Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu
290 295 300

Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu
305 310 315 320

Ser Leu Pro Ile Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr
325 330 335

Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp
340 345 350

Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val
355 360 365

Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr
370 375 380

Phe Ser Leu Thr Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu
385 390 395 400

Lys Lys Asp Arg Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys
405 410 415

Arg Lys Asn Ala Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser

420 425 430

Ser Ser Trp Ser Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly
435 440 445

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val
450 455 460

Ala Thr Pro Asp Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn
465 470 475 480

Leu Leu Arg Ala Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu
485 490 495

Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr
500 505 510

Lys Asp Lys Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr
515 520 525

Lys Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn
530 535 540

Gly Ser Cys Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys
545 550 555 560

Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys
565 570 575

Thr Met Asn Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu
580 585 590

Asp Gln Asn Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn
595 600 605

Phe Asn Ser Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp
610 615 620

Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg

625 630 635 640

Ile Arg Ala Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
645 650 655

<210> 730
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 730
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

```
Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145                 150                 155                 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
                165                 170                 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
            180                 185                 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
        195                 200                 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
    210                 215                 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225                 230                 235                 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
                245                 250                 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
            260                 265                 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
                325                 330                 335

Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro Asp
            340                 345                 350
```

```
Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala
        355                 360                 365

Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro
    370                 375                 380

Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr
385                 390                 395                 400

Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser
                405                 410                 415

Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu
            420                 425                 430

Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile
        435                 440                 445

Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala
    450                 455                 460

Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met
465                 470                 475                 480

Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu
                485                 490                 495

Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr
            500                 505                 510

Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val
        515                 520                 525

Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser Ala Arg Asn Arg
    530                 535                 540

Gln Lys Arg Ser Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly
545                 550                 555                 560
```

Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly
565 570 575

Met Leu Gly Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys
580 585 590

Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu
595 600 605

Glu Gly Val Ala Gln Met Ser Val Gly Gln Gly Ala Lys Leu Thr Ile
610 615 620

Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro
625 630 635 640

Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
645 650 655

<210> 731
<211> 651
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 731
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys

65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
165 170 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg

```
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
                325                 330                 335

Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro Asp
            340                 345                 350

Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala
        355                 360                 365

Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro
    370                 375                 380

Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr
385                 390                 395                 400

Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser
                405                 410                 415

Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu
            420                 425                 430

Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile
        435                 440                 445

Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala
    450                 455                 460

Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met
465                 470                 475                 480

Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu
```

485 490 495

Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr
500 505 510

Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val
515 520 525

Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser Gly Gly Ser Gly
530 535 540

Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro
545 550 555 560

Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly Asp
565 570 575

Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe
580 585 590

Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala
595 600 605

Gln Met Ser Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp Tyr
610 615 620

Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr
625 630 635 640

Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
645 650

<210> 732
<211> 540
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 732

```
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1               5                  10                  15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
            20                  25                  30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
        35                  40                  45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
    50                  55                  60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65                  70                  75                  80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
                85                  90                  95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
            100                 105                 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
        115                 120                 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
    130                 135                 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145                 150                 155                 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
                165                 170                 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
            180                 185                 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
        195                 200                 205
```

```
Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
    210                 215                 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225                 230                 235                 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
                245                 250                 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
            260                 265                 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
                325                 330                 335

Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro Asp
            340                 345                 350

Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala
        355                 360                 365

Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro
    370                 375                 380

Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr
385                 390                 395                 400

Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser
                405                 410                 415
```

```
Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu
            420                 425                 430


Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile
        435                 440                 445


Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala
    450                 455                 460


Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met
465                 470                 475                 480


Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu
                485                 490                 495


Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr
            500                 505                 510


Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val
        515                 520                 525


Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
    530                 535                 540


<210> 733
<211> 710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 733
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1               5                   10                  15


Ala Ser Pro Leu Val Ala Ile Ser Leu Ile Ala Ala Leu Ala Val Asp
            20                  25                  30


Tyr Val Ile Gly Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp
```

```
        35                  40                  45

Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met Gly
    50                  55                  60

Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn
65                  70                  75                  80

Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val
                85                  90                  95

Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile
            100                 105                 110

Met Val Ile Gly Gly Gly Arg Val Ile Glu Gln Phe Leu Pro Lys Ala
        115                 120                 125

Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr
    130                 135                 140

His Phe Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu
145                 150                 155                 160

Phe His Asp Ala Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile
                165                 170                 175

Leu Glu Arg Arg Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys
            180                 185                 190

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
        195                 200                 205

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
    210                 215                 220

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
225                 230                 235                 240

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
```

```
                245                 250                 255

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
            260                 265                 270

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
        275                 280                 285

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
    290                 295                 300

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
305                 310                 315                 320

Asp Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln
                325                 330                 335

Gly Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
            340                 345                 350

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
        355                 360                 365

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
    370                 375                 380

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
385                 390                 395                 400

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
                405                 410                 415

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
            420                 425                 430

Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln
        435                 440                 445

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
```

```
    450                 455                 460

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
465                 470                 475                 480

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
                485                 490                 495

Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            500                 505                 510

Ser Arg Asn Leu Pro Val Ala Thr Pro Asp Pro Gly Met Phe Pro Cys
        515                 520                 525

Leu His His Ser Gln Asn Leu Leu Arg Ala Val Ser Asn Met Leu Gln
    530                 535                 540

Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile
545                 550                 555                 560

Asp His Glu Asp Ile Thr Lys Asp Lys Thr Ser Thr Val Glu Ala Cys
                565                 570                 575

Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser Cys Leu Asn Ser Arg Glu
            580                 585                 590

Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu Ala Ser Arg Lys Thr Ser
        595                 600                 605

Phe Met Met Ala Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met
    610                 615                 620

Tyr Gln Val Glu Phe Lys Thr Met Asn Ala Lys Leu Leu Met Asp Pro
625                 630                 635                 640

Lys Arg Gln Ile Phe Leu Asp Gln Asn Met Leu Ala Val Ile Asp Glu
                645                 650                 655

Leu Met Gln Ala Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser
```

660 665 670

Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile
675 680 685

Leu Leu His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met
690 695 700

Ser Tyr Leu Asn Ala Ser
705 710

<210> 734
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 734
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Val Gly Ser Leu Asn Cys Ile Val Ala Val
20 25 30

Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro
35 40 45

Leu Arg Asn Glu Phe Arg Tyr Phe Phe Arg Met Thr Thr Thr Ser Ser
50 55 60

Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe
65 70 75 80

Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val
85 90 95

Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser
100 105 110

```
Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala
        115                 120                 125

Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys
    130                 135                 140

Glu Phe Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile
145                 150                 155                 160

Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu
                165                 170                 175

Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln
            180                 185                 190

Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
        195                 200                 205

Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys Ile Trp Glu Leu
    210                 215                 220

Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro
225                 230                 235                 240

Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile
                245                 250                 255

Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly Ser Gly Lys Thr
            260                 265                 270

Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys
        275                 280                 285

His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu Leu Leu His Lys
    290                 295                 300

Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu
305                 310                 315                 320
```

```
Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly
               325                 330                 335

Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe
            340                 345                 350

Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln Gly Val Thr Cys
        355                 360                 365

Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly Asp Asn Lys Glu
    370                 375                 380

Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala
385                 390                 395                 400

Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala Val His Lys Leu
               405                 410                 415

Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys
            420                 425                 430

Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg
        435                 440                 445

Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp Ser Thr Pro His
    450                 455                 460

Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln Gly Lys Ser Lys
465                 470                 475                 480

Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr Ser Ala Thr Val
               485                 490                 495

Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr
            500                 505                 510

Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro Cys Ser Gly Gly
        515                 520                 525
```

```
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu
    530                 535                 540

Pro Val Ala Thr Pro Asp Pro Gly Met Phe Pro Cys Leu His His Ser
545                 550                 555                 560

Gln Asn Leu Leu Arg Ala Val Ser Asn Met Leu Gln Lys Ala Arg Gln
                565                 570                 575

Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp
            580                 585                 590

Ile Thr Lys Asp Lys Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu
        595                 600                 605

Leu Thr Lys Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile
    610                 615                 620

Thr Asn Gly Ser Cys Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala
625                 630                 635                 640

Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu
                645                 650                 655

Phe Lys Thr Met Asn Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile
            660                 665                 670

Phe Leu Asp Gln Asn Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala
        675                 680                 685

Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu
    690                 695                 700

Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala
705                 710                 715                 720

Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn
                725                 730                 735
```

Ala Ser

<210> 735
<211> 659
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 735
Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg

145 150 155 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
165 170 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
325 330 335

Gly Ser Gly Gly Gly Gly Ser Arg Asn Leu Pro Val Ala Thr Pro Asp
340 345 350

Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg Ala

```
        355                 360                 365

Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro
    370                 375                 380

Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys Thr
385                 390                 395                 400

Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu Ser
                405                 410                 415

Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys Leu
            420                 425                 430

Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser Ile
        435                 440                 445

Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn Ala
    450                 455                 460

Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn Met
465                 470                 475                 480

Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser Glu
                485                 490                 495

Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr
            500                 505                 510

Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala Val
        515                 520                 525

Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser Glu Ser Arg Arg
    530                 535                 540

Val Arg Arg Asn Lys Arg Ser Lys Gly Val Gln Val Glu Thr Ile Ser
545                 550                 555                 560

Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val
```

565 570 575

His Tyr Thr Gly Met Leu Gly Asp Gly Lys Lys Val Asp Ser Ser Arg
580 585 590

Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile
595 600 605

Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Gly Ala
610 615 620

Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro
625 630 635 640

Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu
645 650 655

Glu Leu Glu

<210> 736
<211> 66
<212> DNA
<213> Homo sapiens

<400> 736
atgtgtcacc agcagttggt catctcttgg ttttccctgg tttttctggc atctcccctc 60

gtggcc 66

<210> 737
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 737
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atcccctctg 60

gtggca 66

<210> 738
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 738
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc cagccctctg 60

gtggcc 66

<210> 739
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 739
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc aagccctctg 60

gtggca 66

<210> 740
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 740
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atccccactg 60

gtggca 66

<210> 741
<211> 66
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 741
atgtgccacc aacagctcgt gatcagctgg ttctccctgg tgttcctggc tagccccctg 60

gtggcc 66

<210> 742
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 742
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc ctccccccctg 60

gtggcc 66

<210> 743
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 743
atgtgccacc agcagctggt catctcctgg ttctctctgg tgtttctggc atctcctctg 60

gtggca 66

<210> 744
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 744
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc atccccactg 60

gtggca 66

<210> 745
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
spacer

<400> 745
Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

<210> 746
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
spacer

<400> 746
gcaaccaatt ttagtctact taaacaagca ggtgatgtag aagaaaatcc aggtcca 57

<210> 747
<211> 306
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 747
Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
1 5 10 15

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
20 25 30

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly

```
        35                  40                  45

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
    50                  55                  60

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
65                  70                  75                  80

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
                85                  90                  95

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
            100                 105                 110

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
        115                 120                 125

Asp Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln
    130                 135                 140

Gly Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
145                 150                 155                 160

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
                165                 170                 175

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
            180                 185                 190

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
        195                 200                 205

Asp Ile Ile Lys Pro Asp Pro Pro Asn Asn Leu Gln Leu Lys Pro Leu
    210                 215                 220

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
225                 230                 235                 240

Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln
```

245 250 255

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
260 265 270

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
275 280 285

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
290 295 300

Cys Ser
305

<210> 748
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 748
atatgggaac tgaagaaaga tgtttatgtc gtagaattgg attggtatcc ggatgcccct 60

ggagaaatgg tggtcctcac ctgtgacacc cctgaagaag atggtatcac ctggaccttg 120

gaccagagca gtgaggtctt aggctctggc aaaaccctga ccatccaagt caaagagttt 180

ggagatgctg gccagtacac ctgtcacaaa ggaggcgagg ttctaagcca ttcgctcctg 240

ctgcttcaca aaaaggaaga tggaatttgg tccactgata ttttaaagga ccagaaagaa 300

cccaaaaata agacctttct aagatgcgag gccaagaatt attctggacg tttcacctgc 360

tggtggctga cgacaatcag tactgatttg acattcagtg tcaaaagcag cagaggctct 420

tctgaccccc aaggggtgac gtgcggagct gctacactct ctgcagagag agtcagaggg 480

gacaacaagg agtatgagta ctcagtggag tgccaggagg acagtgcctg cccagctgct 540

gaggagagtc tgcccattga ggtcatggtg gatgccgttc acaagctcaa gtatgaaaac 600

tacaccagca gcttcttcat cagggacatc atcaaacctg acccacccaa caacttgcag 660

ctgaagccat taaagaattc tcggcaggtg gaggtcagct gggagtaccc tgacacctgg 720

agtactccac attcctactt ctccctgaca ttctgcgttc aggtccaggg caagagcaag 780

agagaaaaga aagatagagt cttcaccgac aagacctcag ccacggtcat ctgccgcaaa 840

aatgccagca ttagcgtgcg ggcccaggac cgctactata gctcatcttg gagcgaatgg 900

gcatctgtgc cctgcagt 918

<210> 749
<211> 432
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 749
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagctaccca 60

tacgatgttc cagattacgc taactgggtg aacgtgatct ccgacctgaa aaagatcgag 120

gatttgatcc agagcatgca cattgacgcc accctgtata ccgagtccga cgtgcacccg 180

agttgcaagg tgactgccat gaagtgcttc ctgctggagc tgcaagtgat cagcctggag 240

agcggcgacg ccagcatcca cgacaccgtg gaaaacctta tcattctggc caacaatagc 300

ctgagcagca acggcaacgt gaccgaaagc ggatgtaagg aatgcgagga actggaagag 360

aagaatatca aagaattcct gcaaagcttc gtgcacatcg tgcagatgtt catcaacact 420

tctggatcct ga 432

<210> 750
<211> 27
<212> DNA
<213> Homo sapiens

<400> 750
agcgccagga atcgccagaa gcggtcc 27

<210> 751
<211> 24
<212> DNA
<213> Homo sapiens

<400> 751

gcccggaata gacagaagag atct 24

<210> 752
<211> 921
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 752
atatgggaac tgaagaaaga tgtttatgtc gtagaattgg attggtatcc ggatgcccct 60

ggagaaatgg tggtcctcac ctgtgacacc cctgaagaag atggtatcac ctggaccttg 120

gaccagagca gtgaggtctt aggctctggc aaaaccctga ccatccaagt caaagagttt 180

ggagatgctg gccagtacac ctgtcacaaa ggaggcgagg ttctaagcca ttcgctcctg 240

ctgcttcaca aaaaggaaga tggaatttgg tccactgata ttttaaagga ccagaaagaa 300

cccaaaaata agacctttct aagatgcgag gccaagaatt attctggacg tttcacctgc 360

tggtggctga cgacaatcag tactgatttg acattcagtg tcaaaagcag cagaggctct 420

tctgaccccc aaggggtgac gtgcggagct gctacactct ctgcagagag agtcagaggg 480

gacaacaagg agtatgagta ctcagtggag tgccaggagg acagtgcctg cccagctgct 540

gaggagagtc tgcccattga ggtcatggtg gatgccgttc acaagctcaa gtatgaaaac 600

tacaccagca gcttcttcat cagggacatc atcaaacctg acccacccaa gaacttgcag 660

ctgaagccat taaagaattc tcggcaggtg gaggtcagct gggagtaccc tgacacctgg 720

agtactccac attcctactt ctccctgaca ttctgcgttc aggtccaggg caagagcaag 780

agagaaaaga aagatagagt cttcacggac aagacctcag ccacggtcat ctgccgcaaa 840

aatgccagca ttagcgtgcg ggcccaggac cgctactata gctcatcttg gagcgaatgg 900

gcatctgtgc cctgcagtta g 921

<210> 753
<211> 918
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
payload

<400> 753
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagtcta gcgaggtgct gggcagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatttgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gcggtgcgag gccaagaatt atagcggccg gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtcctc taggggcagc 420

tccgaccccc agggcgtgac atgcggagca gccaccctgt ccgccgagag ggtgcgcggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tccagcagca 540

gaggagagcc tgcctatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacatcta gcttctttat ccgggacatc atcaagcccg atccacccaa gaacctgcag 660

ctgaagcctc tgaagaattc tagacaggtg gaggtgagct gggagtaccc agacacctgg 720

tccacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagagcaag 780

agggagaaga aggaccgcgt gttcaccgat aagacatccg ccaccgtgat ctgtaggaag 840

aacgcctcca tctctgtgag ggcccaggat cgctactatt cctctagctg gtccgagtgg 900

gcctctgtgc cctgtagc 918

<210> 754
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 754
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca ccagaggagg atggcatcac ctggacactg 120

gatcagtcta gcgaggtgct gggcagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatttgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gcggtgcgag gccaagaatt atagcggccg gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtcctc taggggcagc 420

tccgaccccc agggcgtgac atgcggagca gccaccctgt ccgccgagag ggtgcgcggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tccagcagca 540

gaggagagcc tgcctatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacatcta gcttctttat ccgggacatc atcaagcccg atccacccaa gaacctgcag 660

ctgaagcctc tgaagaattc tagacaggtg gaggtgagct gggagtaccc agacacctgg 720

tccacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagtccaag 780

agggagaaga aggaccgcgt gttcaccgat aagacatctg ccaccgtgat ctgtaggaag 840

aacgcctcca tctctgtgag ggcccaggat cgctactatt cctctagctg gtccgagtgg 900

gcctctgtgc cctgtagc 918

<210> 755
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 755
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagtcta gcgaggtgct gggctccggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatctgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gaggtgcgag gccaagaatt atagcggccg ctttacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtcctc taggggcagc 420

tccgaccccc agggcgtgac atgcggagca gccaccctgt ccgccgagcg ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tccagcagca 540

gaggagagcc tgcctatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacatcta gcttctttat cagggacatc atcaagcccg atccacccaa gaacctgcag 660

ctgaagcctc tgaagaattc tcgccaggtg gaggtgagct gggagtaccc agacacctgg 720

agcacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagtctaag 780

cgggagaaga aggacagagt gttcaccgat aagacaagcg ccaccgtgat ctgtcggaag 840

aacgcctcca tctctgtgcg ggcccaggat agatactatt cctctagctg gtccgagtgg 900

gcctctgtgc cctgtagc 918

<210> 756
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 756
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagagct ccgaggtgct gggaagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatttgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gaggtgcgag gccaagaatt atagcggccg ctttacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtctag cagaggctcc 420

tctgaccccc agggcgtgac atgcggagca gccaccctgt ccgccgagcg ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tcctgcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacaagct ccttctttat cagggacatc atcaagcctg atccccctaa gaacctgcag 660

ctgaagccac tgaagaattc tcgccaggtg gaggtgagct gggagtaccc agacacctgg 720

tccacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagagcaag 780

agggagaaga aggaccgcgt gttcaccgat aagacatccg ccaccgtgat ctgtcggaag 840

aacgcctcca tctctgtgcg ggcccaggat agatactatt ctagctcctg gtccgagtgg 900

gcctctgtgc cctgtagc 918

<210> 757
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 757
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagagct ccgaggtgct gggaagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatttgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gcggtgcgag gccaagaatt atagcggccg gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtctag ccggggctcc 420

tctgacccac agggagtgac atgcggagca gccaccctgt ccgccgagcg ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tcctgcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacaagct ccttctttat cagggacatc atcaagcctg atcccctaa gaacctgcag 660

ctgaagccac tgaagaattc tcgccaggtg gaggtgagct gggagtaccc agacacctgg 720

tccacacccc actcttattt cagcctgacc ttttgcgtgc aggtgcaggg caagtccaag 780

cgggagaaga aggacagagt gttcaccgat aagacatctg ccaccgtgat ctgtcggaag 840

aacgcctcca tctctgtgag ggcccaggat cgctactatt ctagctcctg gagcgagtgg 900

gcatccgtgc catgttct 918

<210> 758
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 758
atctgggagc tcaagaaaga cgtgtacgtg gtggaactgg actggtaccc cgacgcccct 60

ggcgaaatgg tggtgctgac atgcgacacc cctgaggagg atggcattac ctggaccctc 120

gatcagagct ccgaggtgct gggcagcggc aaaaccctga ccatccaggt gaaggagttt 180

ggcgatgccg gccagtacac atgtcacaag ggcggcgagg tgctgagcca ctccctgctg 240

ctgctccaca agaaggaaga tggcatctgg agcaccgaca ttctgaagga tcagaaggag 300

cccaagaaca agacattcct gaggtgtgag gccaagaact acagcggcag gtttacctgc 360

tggtggctga caacaatcag caccgacctc acattctccg tcaagtcctc caggggttct 420

tccgaccctc aaggcgtgac atgcggcgct gccaccctga gcgctgagag agtcaggggc 480

gacaacaagg agtacgagta cagcgtcgaa tgtcaggagg acagcgcctg tcccgccgct 540

gaagagagcc tgcctatcga ggtgatggtg gacgccgtgc acaaactgaa gtatgagaat 600

tacacctcca gcttcttcat cagggacatc atcaaacccg atccccccaa gaacctgcag 660

ctgaagcctc tgaagaacag cagacaggtc gaagtgtcct gggagtaccc tgatacctgg 720

tccacacccc acagctactt cagcctgacc ttttgcgtgc aggtgcaggg caagagcaaa 780

agggagaaga aggacagggt gtttaccgac aagacctccg ccacagtgat ttgcagaaag 840

aacgcctcca tcagcgtgag ggcccaggac aggtattaca gcagctcctg gagcgaatgg 900

gctagcgtgc cctgtagc 918

<210> 759
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 759
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cccgaggagg atggcatcac ctggacactg 120

gatcagtcta gcgaggtgct gggctccggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac ctgtcacaag ggcggcgagg tgctgtccca ctctctgctg 240

ctgctgcaca agaaggagga cggcatctgg tctacagaca tcctgaagga tcagaaggag 300

cctaagaaca agaccttcct gcggtgcgag gccaagaatt atagcggccg gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtcctc tcggggcagc 420

tccgacccac agggagtgac atgcggagca gccaccctgt ccgccgagag ggtgcgcggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tccagcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacatcta gcttctttat ccgggacatc atcaagcccg atccccctaa gaacctgcag 660

ctgaagcctc tgaagaattc tagacaggtg gaggtgagct gggagtaccc cgacacctgg 720

agcacacctc acagctattt ctccctgacc ttttgcgtgc aggtgcaggg caagtccaag 780

agggagaaga aggaccgcgt gttcaccgat aagacatctg ccaccgtgat ctgtcggaag 840

aacgccagca tctccgtgag ggcccaggat cgctactatt cctctagctg gtctgagtgg 900

gccagcgtgc cctgttcc 918

<210> 760
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 760
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc tgatgcccca 60

ggcgagatgg tggtgctgac atgcgacacc cccgaggagg atggcatcac atggaccctg 120

gatcagtcct ctgaggtgct gggctccggc aagacactga ccatccaggt gaaggagttc 180

ggcgacgccg gccagtacac ctgtcacaag ggaggagagg tgctgagcca ctccctgctg 240

ctgctgcaca agaaggagga cggcatctgg tccaccgaca tcctgaagga tcagaaggag 300

cccaagaaca agacattcct gagatgcgag gccaagaatt atagcggcag gtttacctgt 360

tggtggctga caaccatctc cacagatctg acctttttctg tgaagagctc ccggggctct 420

agcgaccctc agggagtgac ctgcggagca gccacactgt ccgccgagcg ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tcctgcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacctcct ctttctttat cagagacatc atcaagccag atcctccaaa gaacctgcag 660

ctgaagcccc tgaagaatag caggcaggtg gaggtgtcct gggagtaccc agacacatgg 720

agcacccccc acagctattt ctccctgaca ttttgcgtgc aggtgcaggg caagtccaag 780

cgcgagaaga aggaccgggt gttcacagat aagacctctg ccacagtgat ctgtcgcaag 840

aacgcctcta tcagcgtgcg cgcccaggat cggtactata gctcctcttg gtctgagtgg 900

gccagcgtgc cttgttcc 918

<210> 761
<211> 918
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 761
atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc cgatgcccct 60

ggcgagatgg tggtgctgac ctgcgacaca cctgaggagg atggcatcac ctggacactg 120

gatcagagct ccgaggtgct gggcagcggc aagaccctga caatccaggt gaaggagttc 180

ggcgacgccg gccagtacac atgtcacaag ggcggcgagg tgctgtctca cagcctgctg 240

ctgctgcaca agaaggagga cggcatctgg tccacagaca tcctgaagga tcagaaggag 300

ccaaagaaca agaccttcct gaggtgcgag gccaagaatt attctggcag gttcacctgt 360

tggtggctga ccacaatcag caccgatctg acattttccg tgaagtctag ccggggctcc 420

tctgaccccc agggagtgac atgcggagca gccaccctgt ccgccgagag ggtgagaggc 480

gataacaagg agtacgagta ttccgtggag tgccaggagg actctgcctg tcctgcagca 540

gaggagagcc tgccaatcga agtgatggtg gatgccgtgc acaagctgaa gtacgagaat 600

tatacaagct ccttctttat cagggacatc atcaagcctg atccccctaa gaacctgcag 660

ctgaagccac tgaagaattc tagacaggtg gaggtgagct gggagtaccc agacacctgg 720

agcacacccc actcctattt ctctctgacc ttttgcgtgc aggtgcaggg caagagcaag 780

agggagaaga aggacagagt gttcaccgat aagacatccg ccaccgtgat ctgtcggaag 840

aacgcctcca tctctgtgcg ggcccaggat cgctactatt ctagctcctg gagcgagtgg 900

gcatccgtgc catgttct 918

<210> 762
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 762
agaaacctcc ccgtggccac tccagaccca ggaatgttcc catgccttca ccactcccaa 60

aacctgctga gggccgtcag caacatgctc cagaaggcca gacaaactct agaattttac 120

ccttgcactt ctgaagagat tgatcatgaa gatatcacaa aagataaaac cagcacagtg 180

gaggcctgtt taccattgga attaaccaag aatgagagtt gcctaaattc cagagagacc 240

tctttcataa ctaatgggag ttgcctggcc tccagaaaga cctcttttat gatggccctg 300

tgccttagta gtatttatga agacttgaag atgtaccagg tggagttcaa gaccatgaat 360

gcaaagcttc tgatggatcc taagaggcag atctttctag atcaaaacat gctggcagtt 420

attgatgagc tgatgcaggc cctgaatttc aacagtgaga ctgtgccaca aaaatcctcc 480

cttgaagaac cggatttta taaaactaaa atcaagctct gcatacttct tcatgctttc 540

agaattcggg cagtgactat tgatagagtg atgagctatc tgaatgcttc ctaa 594

<210> 763
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 763
cgcaatctgc cagtggccac ccctgaccca ggcatgttcc cctgcctgca ccacagccag 60

aacctgctga gggccgtgtc caatatgctg cagaaggccc gccagacact ggagttttac 120

ccttgtacct ctgaggagat cgaccacgag gatatcacaa aggataagac cagcacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagtcct gtctgaacag ccgggaaacc 240

agcttcatca ccaacggctc ctgcctggcc tctcgcaaga ccagcttcat gatggccctg 300

tgcctgtcct ctatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagcggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aatagcgaga cagtgccaca gaagagctcc 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

cggatcagag ccgtgaccat cgacagagtg atgtcctatc tgaatgcctc ttga 594

<210> 764
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 764
cgcaatctgc cagtggccac ccctgaccca ggcatgttcc cctgcctgca ccacagccag 60

aacctgctga gggccgtgtc caatatgctg cagaaggccc gccagacact ggagttttac 120

ccttgtacca gcgaggagat cgaccacgag gatatcacaa aggataagac ctccacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagtcct gtctgaacag ccgggaaacc 240

agcttcatca ccaacggctc ctgcctggcc tctcgcaaga ccagcttcat gatggccctg 300

tgcctgtcct ctatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagcggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aatagcgaga cagtgccaca gaagagctcc 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

cggatcagag ccgtgaccat cgacagagtg atgtcctatc tgaatgcctc ttga 594

<210> 765
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 765
agaaatctgc cagtggccac ccctgaccca ggcatgttcc cctgcctgca ccactctcag 60

aacctgctgc gggccgtgag caatatgctg cagaaggcca gacagacact ggagttttac 120

ccttgtacct ccgaggagat cgaccacgag gatatcacaa aggataagac ctctacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagtcct gtctgaacag ccgggaaacc 240

agcttcatca ccaacggctc ctgcctggcc tctagaaaga ccagcttcat gatggccctg 300

tgcctgtcct ctatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagaggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aatagcgaga cagtgccaca gaagagctcc 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

aggatccgcg ccgtgaccat cgaccgcgtg atgtcctatc tgaatgcctc ttga 594

<210> 766
<211> 591
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 766
agaaatctgc cagtggcaac ccctgaccca ggaatgttcc cttgcctgca ccacagccag 60

aacctgctgc gggccgtgtc caatatgctg cagaaggcca gacagacact ggagttttac 120

ccttgtacct ctgaggagat cgaccacgag gatatcacaa aggataagac cagcacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagtcct gtctgaacag ccgggaaacc 240

agcttcatca ccaacggctc ctgcctggcc tctcgcaaga ccagcttcat gatggccctg 300

tgcctgtcta gcatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagaggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aatagcgaga cagtgccaca gaagtcctct 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

aggatccgcg ccgtgaccat cgacagagtg atgtcctatc tgaacgcctc t 591

<210> 767
<211> 591
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 767
agaaatctgc cagtggcaac ccctgaccca ggaatgttcc cttgcctgca ccacagccag 60

aacctgctga gggccgtgtc caatatgctg cagaaggccc gccagacact ggagttttac 120

ccttgtacca gcgaggagat cgaccacgag gatatcacaa aggataagac ctccacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagagct gtctgaattc ccgggagaca 240

tctttcatca ccaacggcag ctgcctggcc tccagaaaga catcttttat gatggccctg 300

tgcctgtcta gcatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagaggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aatagcgaga cagtgccaca gaagtcctct 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

aggatccgcg ccgtgaccat cgaccgcgtg atgtcttatc tgaacgcatc c 591

<210> 768
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 768
agaaacctgc ctgtcgctac ccccgacccc ggaatgttcc cctgcctgca ccactcccag 60

aacctcctga gggccgtgtc caacatgctg cagaaggcta gacagaccct cgaattctac 120

ccctgtacca gcgaggagat cgaccatgag gacatcacca aggataagac cagcaccgtg 180

gaggcttgcc tgcctctgga gctgaccaaa aacgagagct gcctgaacag cagggaaacc 240

agcttcatta ccaacggctc ctgcctggcc tccaggaaga catccttcat gatggccctg 300

tgcctcagca gcatctacga ggacctgaag atgtatcagg tggagtttaa gaccatgaat 360

gccaagctgc tgatggaccc taagaggcag atcttcctgg accagaatat gctggccgtg 420

attgacgagc tgatgcaggc cctcaacttt aacagcgaga ccgtgcccca gaaaagcagc 480

ctcgaagagc ctgacttcta caaaaccaag attaagctgt gtatcctgct gcacgccttc 540

aggatcaggg ccgtgaccat cgacagggtg atgagctacc tgaacgccag ctaa 594

<210> 769
<211> 597
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 769
agaaatctgc cagtggccac ccctgaccca ggcatgttcc cctgcctgca ccacagccag 60

aacctgctga gggccgtgtc caatatgctg cagaaggccc gccagacact ggagttttac 120

ccctgtacca gcgaggagat cgaccacgag gatatcacaa aggataagac ctccacagtg 180

gaggcctgcc tgcctctgga gctgaccaag aacgagtctt gtctgaatag cagggagaca 240

tccttcatca ccaacggctc ttgcctggcc agccgcaaga catcctttat gatggccctg 300

tgcctgtcct ctatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagaggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aattccgaga cagtgcctca gaagagctcc 480

ctggaggagc cagatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttt 540

cggatcagag ccgtgaccat cgaccgcgtg atgtcttatc tgaatgccag cggatcc 597

<210> 770
<211> 597
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 770
cggaatctgc ctgtggcaac ccccgaccct ggaatgttcc catgcctgca ccacagccag 60

aacctgctgc gcgccgtgtc caatatgctg cagaaggccc ggcagaccct ggagttttac 120

ccatgtacaa gcgaggagat cgaccacgag gatatcacca aggataagac atccaccgtg 180

gaggcatgcc tgccactgga gctgacaaag aacgagtctt gtctgaacag ccgggagaca 240

agcttcatca caaacggctc ttgcctggcc agccggaaga cctcctttat gatggccctg 300

tgcctgagct ccatctacga ggacctgaag atgtatcagg tggagttcaa gacaatgaac 360

gccaagctgc tgatggaccc caagcgccag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttt aatagcgaga cagtgcccca gaagtctagc 480

ctggaggagc ctgatttcta caagacaaag atcaagctgt gcatcctgct gcacgccttc 540

cggatcagag ccgtgaccat cgacagagtg atgtcttatc tgaatgccag cggatcc 597

<210> 771
<211> 591
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 771
cgcaatctgc cagtggcaac ccctgaccca ggaatgttcc cttgcctgca ccacagccag 60

aacctgctgc gggccgtgtc caatatgctg cagaaggccc gccagacact ggagttttac 120

ccttgtacct ctgaggagat cgaccacgag gatatcacaa aggataagac cagcacagtg 180

gaggcctgcc tgccactgga gctgaccaag aacgagagct gtctgaattc cagggagaca 240

tctttcatca ccaacggcag ctgcctggcc tccagaaaga catcttttat gatggccctg 300

tgcctgtcta gcatctacga ggacctgaag atgtatcagg tggagttcaa gaccatgaac 360

gccaagctgc tgatggaccc taagaggcag atctttctgg atcagaatat gctggccgtg 420

atcgacgagc tgatgcaggc cctgaacttc aattccgaga cagtgccaca gaagtcctct 480

ctggaggagc ccgatttcta caagaccaag atcaagctgt gcatcctgct gcacgccttc 540

aggatcaggg ccgtgaccat cgacagagtg atgagctatc tgaacgccag c 591

<210> 772
<211> 477
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 772
atctctctga ttgcggcgct ggcagttgac tacgttattg gcatggaaaa cgcgatgcca 60

tggaacctcc cggctgacct ggcgtggttc aaacgtaaca ccctgaacaa acctgtgatc 120

atgggtcgtc acacctggga atctattggc cgtcctctcc cgggtcgtaa aaacatcatt 180

ctgtcttctc agccaggcac cgacgaccgt gttacctggg ttaaaagcgt tgacgaagcg 240

attgctgcgt gcggtgatgt tcctgaaatt atggtgatcg gcggtggccg tgttatcgaa 300

cagttcctgc cgaaagcgca gaaactgtac ctgacccaca tcgacgcgga agttgaaggt 360

gacacccact tcccggacta cgaaccggat gattgggaga gcgtattctc cgaattccat 420

gatgcggatg cgcaaaactc tcattcttac tgttttgaaa tcctggaacg tcgttga 477

<210> 773
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 773

gtgggcagcc tgaactgtat cgtggccgtg tcccagaaca tgggcatcgg caagaatggc 60

gatctgccat ggccccctct gcggaacgag ttcagatact tctttaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacctg gttttctatc 180

cccgagaaga acagacctct gaagggcagg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgaca 300

gagcagccag agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagt ttatgaatca ccccggccac ctgaagctgt tcgtgaccag aatcatgcag 420

gactttgagt ccgatacatt ctttcctgag atcgatctgg agaagtacaa gctgctgcca 480

gagtatcccg gcgtgctgtc tgacgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaacgat 558

<210> 774
<211> 1959
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 774
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atcccctctg 60

gtggcaggag tgcaggtgga gacaatctct cctggcgatg gccggacctt cccaaagaga 120

ggccagacat gcgtggtgca ctacaccggc atgctggagg acggcaagaa ggtggacagc 180

tcccgggata gaaacaagcc attcaagttt atgctgggca agcaggaagt gatcagggga 240

tgggaggagg gagtggcaca gatgtctgtg ggccagagag ccaagctgac aatcagccct 300

gattacgcat atggagcaac cggacaccca ggaatcatcc cacctcacgc caccctggtg 360

tttgatgtgg agctgctgaa gccagaggga ggatccggag gcatctggga gctgaagaag 420

gacgtgtacg tggtggagct ggactggtat cccgatgccc ctggcgagat ggtggtgctg 480

acctgcgaca cacctgagga ggatggcatc acctggacac tggatcagtc tagcgaggtg 540

ctgggcagcg gcaagaccct gacaatccag gtgaaggagt tcggcgacgc cggccagtac 600

acatgtcaca agggcggcga ggtgctgtct cacagcctgc tgctgctgca caagaaggag 660

gacggcattt ggtccacaga catcctgaag gatcagaagg agccaaagaa caagaccttc 720

ctgcggtgcg aggccaagaa ttatagcggc cggttcacct gttggtggct gaccacaatc 780

agcaccgatc tgacattttc cgtgaagtcc tctaggggca gctccgaccc ccagggcgtg 840

acatgcggag cagccaccct gtccgccgag agggtgcgcg gcgataacaa ggagtacgag 900

tattccgtgg agtgccagga ggactctgcc tgtccagcag cagaggagag cctgcctatc 960

gaagtgatgg tggatgccgt gcacaagctg aagtacgaga attatacatc tagcttcttt 1020

atccgggaca tcatcaagcc cgatccaccc aagaacctgc agctgaagcc tctgaagaat 1080

tctagacagg tggaggtgag ctgggagtac ccagacacct ggtccacacc ccactcttat 1140

ttcagcctga ccttttgcgt gcaggtgcag ggcaagagca agagggagaa gaaggaccgc 1200

gtgttcaccg ataagacatc cgccaccgtg atctgtagga agaacgcctc catctctgtg 1260

agggcccagg atcgctacta ttcctctagc tggtccgagt gggcctctgt gccctgtagc 1320

ggaggaggag gatccggagg aggaggatct ggcggcggcg gcagccgcaa tctgccagtg 1380

gccacccctg acccaggcat gttcccctgc ctgcaccaca gccagaacct gctgagggcc 1440

gtgtccaata tgctgcagaa ggcccgccag acactggagt tttacccttg tacctctgag 1500

gagatcgacc acgaggatat cacaaaggat aagaccagca cagtggaggc ctgcctgcca 1560

ctggagctga ccaagaacga gtcctgtctg aacagccggg aaaccagctt catcaccaac 1620

ggctcctgcc tggcctctcg caagaccagc ttcatgatgg ccctgtgcct gtcctctatc 1680

tacgaggacc tgaagatgta tcaggtggag ttcaagacca tgaacgccaa gctgctgatg 1740

gaccctaagc ggcagatctt tctggatcag aatatgctgg ccgtgatcga cgagctgatg 1800

caggccctga acttcaatag cgagacagtg ccacagaaga gctccctgga ggagcccgat 1860

ttctacaaga ccaagatcaa gctgtgcatc ctgctgcacg cctttcggat cagagccgtg 1920

accatcgaca gagtgatgtc ctatctgaat gcctcttga 1959

<210> 775
<211> 1962
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic construct

<400> 775
atgggcgtgc aggtggagac aatctcccct ggcgatggcc ggaccttccc aaagagaggc 60

cagacatgcg tggtgcacta caccggcatg ctggaggacg gcaagaaggt ggacagctcc 120

cgggatagaa acaagccttt caagtttatg ctgggcaagc aggaagtgat caggggatgg 180

gaggagggag tggcacagat gtctgtgggc cagagagcca agctgacaat cagccctgat 240

tacgcatatg gagcaaccgg acacccagga atcatcccac ctcacgccac cctggtgttt 300

gacgtggagc tgctgaagcc agagggagga tctggaggaa tgtgccacca gcagctggtc 360

atcagctggt tctccctggt gtttctggcc agccctctgg tggccatctg ggagctgaag 420

aaggacgtgt acgtggtgga gctggactgg tatcccgatg cccctggcga gatggtggtg 480

ctgacctgcg acacaccaga ggaggatggc atcacctgga cactggatca gtctagcgag 540

gtgctgggca gcggcaagac cctgacaatc caggtgaagg agttcggcga cgccggccag 600

tacacatgtc acaagggcgg cgaggtgctg tctcacagcc tgctgctgct gcacaagaag 660

gaggacggca tttggtccac agacatcctg aaggatcaga aggagccaaa gaacaagacc 720

ttcctgcggt gcgaggccaa gaattatagc ggccggttca cctgttggtg gctgaccaca 780

atcagcaccg atctgacatt ttccgtgaag tcctctaggg gcagctccga cccccagggc 840

gtgacatgcg gagcagccac cctgtccgcc gagagggtgc gcggcgataa caaggagtac 900

gagtattccg tggagtgcca ggaggactct gcctgtccag cagcagagga gagcctgcct 960

atcgaagtga tggtggatgc cgtgcacaag ctgaagtacg agaattatac atctagcttc 1020

tttatccggg acatcatcaa gcccgatcca cccaagaacc tgcagctgaa gcctctgaag 1080

aattctagac aggtggaggt gagctgggag tacccagaca cctggtccac accccactct 1140

tatttcagcc tgacctttg cgtgcaggtg cagggcaagt ccaagaggga gaagaaggac 1200

cgcgtgttca ccgataagac atctgccacc gtgatctgta ggaagaacgc ctccatctct 1260

gtgagggccc aggatcgcta ctattcctct agctggtccg agtgggcctc tgtgccctgt 1320

agcggaggag gaggatccgg aggaggagga tctggcggcg gcggcagccg caatctgcca 1380

gtggccaccc ctgacccagg catgttcccc tgcctgcacc acagccagaa cctgctgagg 1440

gccgtgtcca atatgctgca gaaggcccgc cagacactgg agttttaccc ttgtaccagc 1500

gaggagatcg accacgagga tatcacaaag gataagacct ccacagtgga ggcctgcctg 1560

ccactggagc tgaccaagaa cgagtcctgt ctgaacagcc gggaaaccag cttcatcacc 1620

aacggctcct gcctggcctc tcgcaagacc agcttcatga tggccctgtg cctgtcctct 1680

atctacgagg acctgaagat gtatcaggtg gagttcaaga ccatgaacgc caagctgctg 1740

atggacccta agcggcagat ctttctggat cagaatatgc tggccgtgat cgacgagctg 1800

atgcaggccc tgaacttcaa tagcgagaca gtgccacaga agagctccct ggaggagccc 1860

gatttctaca agaccaagat caagctgtgc atcctgctgc acgcctttcg gatcagagcc 1920

gtgaccatcg acagagtgat gtcctatctg aatgcctctt ga 1962

<210> 776
<211> 1971
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 776
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc aagccctctg 60

gtggcaggag tgcaggtgga gacaatctcc cctggcgatg gcaggacctt cccaaagcgc 120

ggccagacat gcgtggtgca ctacaccggc atgctggagg acggcaagaa ggtggacagc 180

tcccgggata gaaacaagcc attcaagttt atgctgggca agcaggaagt gatcagggga 240

tgggaggagg gagtggcaca gatgtccgtg ggacagcgcg ccaagctgac aatctctcct 300

gattacgcat atggagcaac cggacaccca ggaatcatcc cacctcacgc caccctggtg 360

tttgacgtgg agctgctgaa gcccgagagc gccaggaatc gccagaagcg gtccatctgg 420

gagctgaaga aggacgtgta cgtggtggag ctggactggt atcccgatgc ccctggcgag 480

atggtggtgc tgacctgcga cacacctgag gaggatggca tcacctggac actggatcag 540

tctagcgagg tgctgggctc cggcaagacc ctgacaatcc aggtgaagga gttcggcgac 600

gccggccagt acacatgtca caagggcggc gaggtgctgt ctcacagcct gctgctgctg 660

cacaagaagg aggacggcat ctggtccaca gacatcctga aggatcagaa ggagccaaag 720

aacaagacct tcctgaggtg cgaggccaag aattatagcg gccgctttac ctgttggtgg 780

ctgaccacaa tcagcaccga tctgacattt tccgtgaagt cctctagggg cagctccgac 840

ccccagggcg tgacatgcgg agcagccacc ctgtccgccg agcgggtgag aggcgataac 900

aaggagtacg agtattccgt ggagtgccag gaggactctg cctgtccagc agcagaggag 960

agcctgccta tcgaagtgat ggtggatgcc gtgcacaagc tgaagtacga gaattataca 1020

tctagcttct ttatcaggga catcatcaag cccgatccac ccaagaacct gcagctgaag 1080

cctctgaaga attctcgcca ggtggaggtg agctgggagt acccagacac ctggagcaca 1140

ccccactctt atttcagcct gacctttgc gtgcaggtgc agggcaagtc taagcgggag 1200

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tccatctctg tgcgggccca ggatagatac tattcctcta gctggtccga gtgggcctct 1320

gtgccctgta gcggaggagg aggatccgga ggaggaggat ctggcggcgg cggcagcaga 1380

aatctgccag tggccacccc tgacccaggc atgttcccct gcctgcacca ctctcagaac 1440

ctgctgcggg ccgtgagcaa tatgctgcag aaggccagac agacactgga gttttaccct 1500

tgtacctccg aggagatcga ccacgaggat atcacaaagg ataagacctc tacagtggag 1560

gcctgcctgc cactggagct gaccaagaac gagtcctgtc tgaacagccg ggaaaccagc 1620

ttcatcacca acggctcctg cctggcctct agaaagacca gcttcatgat ggccctgtgc 1680

ctgtcctcta tctacgagga cctgaagatg tatcaggtgg agttcaagac catgaacgcc 1740

aagctgctga tggaccctaa gaggcagatc tttctggatc agaatatgct ggccgtgatc 1800

gacgagctga tgcaggccct gaacttcaat agcgagacag tgccacagaa gagctccctg 1860

gaggagcccg atttctacaa gaccaagatc aagctgtgca tcctgctgca cgcctttagg 1920

atccgcgccg tgaccatcga ccgcgtgatg tcctatctga atgcctcttg a 1971

<210> 777
<211> 1968
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 777
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atccccactg 60

gtggcaatct gggagctgaa gaaggacgtg tacgtggtgg agctggactg gtatcccgat 120

gcccctggcg agatggtggt gctgacctgc gacacacctg aggaggatgg catcacctgg 180

acactggatc agagctccga ggtgctggga agcggcaaga ccctgacaat ccaggtgaag 240

gagttcggcg acgccggcca gtacacatgt cacaagggcg gcgaggtgct gtctcacagc 300

ctgctgctgc tgcacaagaa ggaggacggc atttggtcca cagacatcct gaaggatcag 360

aaggagccaa agaacaagac cttcctgagg tgcgaggcca agaattatag cggccgcttt 420

acctgttggt ggctgaccac aatcagcacc gatctgacat tttccgtgaa gtctagcaga 480

ggctcctctg acccccaggg cgtgacatgc ggagcagcca ccctgtccgc cgagcgggtg 540

agaggcgata acaaggagta cgagtattcc gtggagtgcc aggaggactc tgcctgtcct 600

gcagcagagg agagcctgcc aatcgaagtg atggtggatg ccgtgcacaa gctgaagtac 660

gagaattata caagctcctt ctttatcagg gacatcatca agcctgatcc ccctaagaac 720

ctgcagctga agccactgaa gaattctcgc caggtggagg tgagctggga gtacccagac 780

acctggtcca caccccactc ttatttcagc ctgacctttt gcgtgcaggt gcagggcaag 840

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cggaagaacg cctccatctc tgtgcgggcc caggatagat actattctag ctcctggtcc 960

gagtgggcct ctgtgccctg tagcggagga ggaggatccg gaggaggagg atctggcgga 1020

ggaggcagca gaaatctgcc agtggcaacc cctgacccag gaatgttccc ttgcctgcac 1080

cacagccaga acctgctgcg ggccgtgtcc aatatgctgc agaaggccag acagacactg 1140

gagttttacc cttgtacctc tgaggagatc gaccacgagg atatcacaaa ggataagacc 1200

agcacagtgg aggcctgcct gccactggag ctgaccaaga acgagtcctg tctgaacagc 1260

cgggaaacca gcttcatcac caacggctcc tgcctggcct ctcgcaagac cagcttcatg 1320

atggccctgt gcctgtctag catctacgag gacctgaaga tgtatcaggt ggagttcaag 1380

accatgaacg ccaagctgct gatggaccct aagaggcaga tctttctgga tcagaatatg 1440

ctggccgtga tcgacgagct gatgcaggcc ctgaacttca atagcgagac agtgccacag 1500

aagtcctctc tggaggagcc cgatttctac aagaccaaga tcaagctgtg catcctgctg 1560

cacgccttta ggatccgcgc cgtgaccatc gacagagtga tgtcctatct gaacgcctct 1620

gcccggaata gacagaagag atctggcgtg caggtggaga caatcagccc cggcgatggc 1680

cggacctttc ctaagagagg ccagacatgc gtggtgcact acaccggcat gctgggcgac 1740

ggcaagaagg tggacagctc cagggatcgc aataagccct tcaagtttat gctgggcaag 1800

caggaagtga tcaggggatg ggaggaggga gtggcacaga tgtccgtggg acagggcgcc 1860

aagctgacaa tctctccaga ttacgcatat ggagcaaccg gacacccagg aatcatccca 1920

ccccacgcca ccctggtgtt cgacgtggag ctgctggagc tggagtga 1968

<210> 778
<211> 1956
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 778
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atccccactg 60

gtggcaatct gggagctgaa gaaggacgtg tacgtggtgg agctggactg gtatcccgat 120

gcccctggcg agatggtggt gctgacctgc gacacacctg aggaggatgg catcacctgg 180

acactggatc agagctccga ggtgctggga agcggcaaga ccctgacaat ccaggtgaag 240

gagttcggcg acgccggcca gtacacatgt cacaagggcg gcgaggtgct gtctcacagc 300

ctgctgctgc tgcacaagaa ggaggacggc atttggtcca cagacatcct gaaggatcag 360

aaggagccaa agaacaagac cttcctgcgg tgcgaggcca agaattatag cggccggttc 420

acctgttggt ggctgaccac aatcagcacc gatctgacat tttccgtgaa gtctagccgg 480

ggctcctctg acccacaggg agtgacatgc ggagcagcca ccctgtccgc cgagcgggtg 540

agaggcgata acaaggagta cgagtattcc gtggagtgcc aggaggactc tgcctgtcct 600

gcagcagagg agagcctgcc aatcgaagtg atggtggatg ccgtgcacaa gctgaagtac 660

gagaattata caagctcctt ctttatcagg gacatcatca agcctgatcc ccctaagaac 720

ctgcagctga agccactgaa gaattctcgc caggtggagg tgagctggga gtacccagac 780

acctggtcca caccccactc ttatttcagc ctgacctttt gcgtgcaggt gcagggcaag 840

tccaagcggg agaagaagga cagagtgttc accgataaga catctgccac cgtgatctgt 900

cggaagaacg cctccatctc tgtgagggcc caggatcgct actattctag ctcctggagc 960

gagtgggcat ccgtgccatg ttctggagga ggaggaagcg gaggaggagg atccggcgga 1020

ggaggctcta gaaatctgcc agtggcaacc cctgacccag gaatgttccc ttgcctgcac 1080

cacagccaga acctgctgag ggccgtgtcc aatatgctgc agaaggcccg ccagacactg 1140

gagttttacc cttgtaccag cgaggagatc gaccacgagg atatcacaaa ggataagacc 1200

tccacagtgg aggcctgcct gccactggag ctgaccaaga acgagagctg tctgaattcc 1260

cgggagacat ctttcatcac caacggcagc tgcctggcct ccagaaagac atcttttatg 1320

atggccctgt gcctgtctag catctacgag gacctgaaga tgtatcaggt ggagttcaag 1380

accatgaacg ccaagctgct gatggaccct aagaggcaga tctttctgga tcagaatatg 1440

ctggccgtga tcgacgagct gatgcaggcc ctgaacttca atagcgagac agtgccacag 1500

aagtcctctc tggaggagcc cgatttctac aagaccaaga tcaagctgtg catcctgctg 1560

cacgccttta ggatccgcgc cgtgaccatc gaccgcgtga tgtcttatct gaacgcatcc 1620

ggaggatctg gaggagtgca ggtggagaca atcagccccg gcgatggcag gacctttcct 1680

aagcgcggcc agacatgcgt ggtgcactac accggcatgc tgggcgacgg caagaaggtg 1740

gacagctccc gggatagaaa taagcccttc aagtttatgc tgggcaagca ggaagtgatc 1800

agaggctggg aggagggagt ggcacagatg tctgtgggac agggcgccaa gctgacaatc 1860

agcccagatt acgcatatgg agcaaccgga cacccaggaa tcatcccacc ccacgccacc 1920

ctggtgttcg acgtggagct gctggagctg gagtga 1956

<210> 779
<211> 1623
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 779

atgtgccacc aacagctcgt gatcagctgg ttctccctgg tgttcctggc tagcccctg 60

gtggccatct gggagctcaa gaaagacgtg tacgtggtgg aactggactg gtaccccgac 120

gcccctggcg aaatggtggt gctgacatgc gacacccctg aggaggatgg cattacctgg 180

accctcgatc agagctccga ggtgctgggc agcggcaaaa ccctgaccat ccaggtgaag 240

gagtttggcg atgccggcca gtacacatgt cacaagggcg gcgaggtgct gagccactcc 300

ctgctgctgc tccacaagaa ggaagatggc atctggagca ccgacattct gaaggatcag 360

aaggagccca agaacaagac attcctgagg tgtgaggcca agaactacag cggcaggttt 420

acctgctggt ggctgacaac aatcagcacc gacctcacat tctccgtcaa gtcctccagg 480

ggttcttccg accctcaagg cgtgacatgc ggcgctgcca ccctgagcgc tgagagagtc 540

aggggcgaca acaaggagta cgagtacagc gtcgaatgtc aggaggacag cgcctgtccc 600

gccgctgaag agagcctgcc tatcgaggtg atggtggacg ccgtgcacaa actgaagtat 660

gagaattaca cctccagctt cttcatcagg gacatcatca aacccgatcc ccccaagaac 720

ctgcagctga agcctctgaa gaacagcaga caggtcgaag tgtcctggga gtaccctgat 780

acctggtcca caccccacag ctacttcagc ctgacctttt gcgtgcaggt gcagggcaag 840

agcaaaaggg agaagaagga cagggtgttt accgacaaga cctccgccac agtgatttgc 900

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gaatgggcta gcgtgccctg tagcggagga ggaggcagcg gaggaggagg ttctggagga 1020

ggcggcagca gaaacctgcc tgtcgctacc cccgaccccg gaatgttccc ctgcctgcac 1080

cactcccaga acctcctgag ggccgtgtcc aacatgctgc agaaggctag acagaccctc 1140

gaattctacc cctgtaccag cgaggagatc gaccatgagg acatcaccaa ggataagacc 1200

agcaccgtgg aggcttgcct gcctctggag ctgaccaaaa acgagagctg cctgaacagc 1260

agggaaacca gcttcattac caacggctcc tgcctggcct ccaggaagac atccttcatg 1320

atggccctgt gcctcagcag catctacgag gacctgaaga tgtatcaggt ggagtttaag 1380

accatgaatg ccaagctgct gatggaccct aagaggcaga tcttcctgga ccagaatatg 1440

ctggccgtga ttgacgagct gatgcaggcc ctcaacttta acagcgagac cgtgccccag 1500

aaaagcagcc tcgaagagcc tgacttctac aaaaccaaga ttaagctgtg tatcctgctg 1560

cacgccttca ggatcagggc cgtgaccatc gacagggtga tgagctacct gaacgccagc 1620

taa 1623

<210> 780
<211> 2130
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 780
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc ctccccctg 60

gtggccatct ctctgatcgc cgccctggcc gtggattacg tgatcggcat ggagaacgcc 120

atgccatgga atctgccagc agacctggca tggttcaaga ggaacacact gaataagcca 180

gtgatcatgg gcagacacac ctgggagtcc atcggccggc cactgccagg cagaaagaac 240

atcatcctga gctcccagcc cggcacagac gatagggtga cctgggtgaa gagcgtggac 300

gaggcaatcg cagcatgcgg cgatgtgcct gagatcatgg tcatcggagg aggacgcgtg 360

atcgagcagt tcctgccaaa ggcccagaag ctgtacctga cacacatcga tgccgaggtg 420

gagggcgaca cccactttcc tgattatgag ccagacgatt gggagtccgt gttctctgag 480

tttcacgacg ccgatgccca gaactctcac agctattgtt ttgagatcct ggagcggaga 540

gagtctaggc gcgtgcggag aaataagcgg agcaagatct gggagctgaa gaaggacgtg 600

tacgtggtgg agctggactg gtatcccgat gcccctggcg agatggtggt gctgacctgc 660

gacacacccg aggaggatgg catcacctgg acactggatc agtctagcga ggtgctgggc 720

tccggcaaga ccctgacaat ccaggtgaag gagttcggcg acgccggcca gtacacctgt 780

cacaagggcg gcgaggtgct gtcccactct ctgctgctgc tgcacaagaa ggaggacggc 840

atctggtcta cagacatcct gaaggatcag aaggagccta agaacaagac cttcctgcgg 900

tgcgaggcca agaattatag cggccggttc acctgttggt ggctgaccac aatcagcacc 960

gatctgacat tttccgtgaa gtcctctcgg ggcagctccg acccacaggg agtgacatgc 1020

ggagcagcca ccctgtccgc cgagagggtg cgcggcgata acaaggagta cgagtattcc 1080

gtggagtgcc aggaggactc tgcctgtcca gcagcagagg agagcctgcc aatcgaagtg 1140

atggtggatg ccgtgcacaa gctgaagtac gagaattata catctagctt ctttatccgg 1200

gacatcatca agcccgatcc ccctaagaac ctgcagctga agcctctgaa gaattctaga 1260

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gaccacgagg atatcacaaa ggataagacc tccacagtgg aggcctgcct gcctctggag 1740

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gacctgaaga tgtatcaggt ggagttcaag accatgaacg ccaagctgct gatggaccct 1920

aagaggcaga tctttctgga tcagaatatg ctggccgtga tcgacgagct gatgcaggcc 1980

ctgaacttca attccgagac agtgcctcag aagagctccc tggaggagcc agatttctac 2040

aagaccaaga tcaagctgtg catcctgctg cacgcctttc ggatcagagc cgtgaccatc 2100

gaccgcgtga tgtcttatct gaatgccagc 2130

<210> 781
<211> 2214
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 781
atgtgccacc agcagctggt catctcctgg ttctctctgg tgtttctggc atctcctctg 60

gtggcagtgg gcagcctgaa ctgtatcgtg gccgtgtccc agaacatggg catcggcaag 120

aatggcgatc tgccatggcc ccctctgcgg aacgagttca gatacttctt taggatgacc 180

acaaccagct ccgtggaggg caagcagaac ctggtcatca tgggcaagaa gacctggttt 240

tctatccccg agaagaacag acctctgaag ggcaggatca atctggtgct gagcagagag 300

ctgaaggagc caccacaggg agcacacttc ctgagccgga gcctggacga tgccctgaag 360

ctgacagagc agccagagct ggccaacaag gtggacatgg tgtggatcgt gggcggctct 420

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atgcaggact ttgagtccga tacattcttt cctgagatcg atctggagaa gtacaagctg 540

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atctgggagc tgaagaagga cgtgtacgtg gtggagctgg actggtatcc tgatgcccca 720

ggcgagatgg tggtgctgac atgcgacacc cccgaggagg atggcatcac atggaccctg 780

gatcagtcct ctgaggtgct gggctccggc aagacactga ccatccaggt gaaggagttc 840

ggcgacgccg gccagtacac ctgtcacaag ggaggagagg tgctgagcca ctccctgctg 900

ctgctgcaca agaaggagga cggcatctgg tccaccgaca tcctgaagga tcagaaggag 960

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ctgaagcccc tgaagaatag caggcaggtg gaggtgtcct gggagtaccc agacacatgg 1380

agcacccccc acagctattt ctccctgaca ttttgcgtgc aggtgcaggg caagtccaag 1440

cgcgagaaga aggaccgggt gttcacagat aagacctctg ccacagtgat ctgtcgcaag 1500

aacgcctcta tcagcgtgcg cgcccaggat cggtactata gctcctcttg gtctgagtgg 1560

gccagcgtgc cttgttccgg cggcggcggc tctggaggag gaggcagcgg cggaggaggc 1620

tcccggaatc tgcctgtggc aacccccgac cctggaatgt tcccatgcct gcaccacagc 1680

cagaacctgc tgcgcgccgt gtccaatatg ctgcagaagg cccggcagac cctggagttt 1740

tacccatgta caagcgagga gatcgaccac gaggatatca ccaaggataa gacatccacc 1800

gtggaggcat gcctgccact ggagctgaca aagaacgagt cttgtctgaa cagccgggag 1860

acaagcttca tcacaaacgg ctcttgcctg gccagccgga agacctcctt tatgatggcc 1920

ctgtgcctga gctccatcta cgaggacctg aagatgtatc aggtggagtt caagacaatg 1980

aacgccaagc tgctgatgga ccccaagcgc cagatctttc tggatcagaa tatgctggcc 2040

gtgatcgacg agctgatgca ggccctgaac tttaatagcg agacagtgcc ccagaagtct 2100

agcctggagg agcctgattt ctacaagaca aagatcaagc tgtgcatcct gctgcacgcc 2160

ttccggatca gagccgtgac catcgacaga gtgatgtctt atctgaatgc cagc 2214

<210> 782
<211> 1980
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 782
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc atccccactg 60

gtggcaatct gggagctgaa gaaggacgtg tacgtggtgg agctggactg gtatcccgat 120

gcccctggcg agatggtggt gctgacctgc gacacacctg aggaggatgg catcacctgg 180

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gagttcggcg acgccggcca gtacacatgt cacaagggcg gcgaggtgct gtctcacagc 300

ctgctgctgc tgcacaagaa ggaggacggc atctggtcca cagacatcct gaaggatcag 360

aaggagccaa agaacaagac cttcctgagg tgcgaggcca agaattattc tggcaggttc 420

acctgttggt ggctgaccac aatcagcacc gatctgacat tttccgtgaa gtctagccgg 480

ggctcctctg acccccaggg agtgacatgc ggagcagcca ccctgtccgc cgagagggtg 540

agaggcgata acaaggagta cgagtattcc gtggagtgcc aggaggactc tgcctgtcct 600

gcagcagagg agagcctgcc aatcgaagtg atggtggatg ccgtgcacaa gctgaagtac 660

gagaattata caagctcctt ctttatcagg gacatcatca agcctgatcc ccctaagaac 720

ctgcagctga agccactgaa gaattctaga caggtggagg tgagctggga gtacccagac 780

acctggagca caccccactc ctatttctct ctgacctttt gcgtgcaggt gcagggcaag 840

agcaagaggg agaagaagga cagagtgttc accgataaga catccgccac cgtgatctgt 900

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ggcggctctc gcaatctgcc agtggcaacc cctgacccag gaatgttccc ttgcctgcac 1080

cacagccaga acctgctgcg ggccgtgtcc aatatgctgc agaaggcccg ccagacactg 1140

gagttttacc cttgtacctc tgaggagatc gaccacgagg atatcacaaa ggataagacc 1200

agcacagtgg aggcctgcct gccactggag ctgaccaaga acgagagctg tctgaattcc 1260

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atggccctgt gcctgtctag catctacgag gacctgaaga tgtatcaggt ggagttcaag 1380

accatgaacg ccaagctgct gatggaccct aagaggcaga tctttctgga tcagaatatg 1440

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aagtcctctc tggaggagcc cgatttctac aagaccaaga tcaagctgtg catcctgctg 1560

cacgccttca ggatcagggc cgtgaccatc gacagagtga tgagctatct gaacgccagc 1620

gagtccagga gagtgcggcg caacaagagg agcaagggcg tgcaggtgga gacaatcagc 1680

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atgctgggcg acggcaagaa ggtggacagc tccagggata gaaacaagcc attcaagttt 1800

atgctgggca agcaggaagt gatcagagga tgggaggagg gagtggcaca gatgtccgtg 1860

ggacagggcg ccaagctgac aatctctcca gattacgcat atggagcaac cggacaccca 1920

ggaatcatcc caccccacgc caccctggtg ttcgacgtgg agctgctgga gctggagtga 1980

<210> 783
<211> 20
<212> PRT
<213> Homo sapiens

<400> 783
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser
            20

<210> 784
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      linker sequence

<400> 784
Glu Phe Ser Thr Glu Phe
1   5

<210> 785
<211> 114
<212> PRT
<213> Homo sapiens

<400> 785
Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1   5   10   15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
            20   25   30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
        35   40   45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
    50   55   60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65   70   75   80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
                85   90   95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
            100   105   110

Thr Ser

<210> 786
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 786
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile
20 25 30

Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu
35 40 45

Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu
50 55 60

Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His
65 70 75 80

Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser
85 90 95

Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu
100 105 110

Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln
115 120 125

Met Phe Ile Asn Thr Ser
130

<210> 787
<211> 303

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 787

```
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                  10                  15

Val Thr Asn Ser Glu Phe Ser Thr Glu Phe Ile Ser Leu Ile Ala Ala
            20                  25                  30

Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala Met Pro Trp Asn
        35                  40                  45

Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro
    50                  55                  60

Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro
65                  70                  75                  80

Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg
                85                  90                  95

Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly Asp
            100                 105                 110

Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Ile Glu Gln Phe
        115                 120                 125

Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu Val
    130                 135                 140

Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser
145                 150                 155                 160

Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser His Ser Tyr
                165                 170                 175
```

Cys Phe Glu Ile Leu Glu Arg Arg Gly Gly Ser Gly Gly Asn Trp Val
180 185 190

Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met
195 200 205

His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys
210 215 220

Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser
225 230 235 240

Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile
245 250 255

Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser
260 265 270

Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe
275 280 285

Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
290 295 300

<210> 788
<211> 60
<212> DNA
<213> Homo sapiens

<400> 788
atgtaccgaa tgcaactgct gagctgcatc gccctgagcc tggcactcgt gaccaacagc 60

<210> 789
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 789
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60

<210> 790
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 790
atgtacagga tgcagctgct gagctgcatc gccctgagcc tggccctggt gaccaacagc 60

<210> 791
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
signal sequence

<400> 791
atgtacagaa tgcagctgct gagctgcatc gccctgtccc tcgccctggt gaccaactcc 60

<210> 792
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 792
gagttcagca ccgagttt 18

<210> 793
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 793
gagttctcca ccgagttc 18

<210> 794
<211> 345
<212> DNA
<213> Homo sapiens

<400> 794
aactgggtga atgtaataag tgatttgaaa aaaattgaag atcttattca atctatgcat 60

attgatgcta ctttatatac ggaaagtgat gttcacccca gttgcaaagt aacagcaatg 120

aagtgctttc tcttggagtt acaagttatt tcacttgagt ccggagatgc aagtattcat 180

gatacagtag aaaatctgat catcctagca aacaacagtt tgtcttctaa tgggaatgta 240

acagaatctg gatgcaaaga atgtgaggaa ctggaggaaa aaaatattaa agaatttttg 300

cagagttttg tacatattgt ccaaatgttc atcaacactt cttga 345

<210> 795
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 795
aactgggtga acgtgatctc cgacctgaag aagatcgagg acctgatcca gtccatgcac 60

atcgacgcca ccctgtacac cgagagcgac gtgcacccta gctgcaaggt gaccgccatg 120

aagtgcttcc tgctggagct gcaggtgatc agcctggaga gcggcgatgc cagcatccac 180

gacacagtgg agaacctgat catcctggcc aacaacagcc tgagcagcaa cggcaatgtg 240

accgagagcg gctgcaagga gtgcgaggag ctggaggaga agaacatcaa ggagttcctg 300

cagtccttcg tgcacatcgt gcagatgttc atcaacacca gctaa 345

<210> 796
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 796
aactgggtca acgtgatcag cgacctgaag aagatcgagg acctcatcca gtccatgcac 60

attgacgcca ccctgtacac cgagtccgat gtgcacccta gctgcaaggt gaccgccatg 120

aaatgcttcc tgctggagct gcaggtcatc tccttagaaa gcggcgatgc ctccatccac 180

gacaccgtgg agaacctgat catcctggcc aataactccc tgagcagcaa cggcaacgtg 240

accgagagcg gctgcaaaga gtgtgaagag ctggaggaga agaacattaa ggagttcctg 300

cagagcttcg tgcacatcgt gcaaatgttc atcaacacca gctaa 345

<210> 797
<211> 342
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 797
aactgggtga acgtgatctc cgacctgaaa aagatcgagg atttgatcca gagcatgcac 60

attgacgcca ccctgtatac cgagtccgac gtgcacccga gttgcaaggt gactgccatg 120

aagtgcttcc tgctggagct gcaagtgatc agcctggaga gcggcgacgc cagcatccac 180

gacaccgtgg aaaaccttat cattctggcc aacaatagcc tgagcagcaa cggcaacgtg 240

accgaaagcg gatgtaagga atgcgaggaa ctggaagaga agaatatcaa agaattcctg 300

caaagcttcg tgcacatcgt gcagatgttc atcaacactt ct 342

<210> 798
<211> 477
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 798
atctctctga ttgcggcgct ggcagttgac cacgttattg gcatggaaaa cgcgatgcca 60

tggaacctcc cggctgacct ggcgtggttc aaacgtaaca ccctgaacaa acctgtgatc 120

atgggtcgtc acacctggga atctattggc cgtcctctcc cgggtcgtaa aaacatcatt 180

ctgtcttctc agccaggcac cgacgaccgt gttacctggg ttaaaagcgt tgacgaagcg 240

attgctgcgt gcggtgatgt tcctgaaatt atggtgatcg gcggtggccg tgtttacgaa 300

cagttcctgc cgaaagcgca gaaactgtac ctgacccaca tcgacgcgga agttgaaggt 360

gacacccact tcccggacta caaaccggat gattgggaga gcgtattctc cgaattccat 420

gatgcggatg cgcaaaactc tcattcttac tgttttgaaa tcctggaacg tcgttga 477

<210> 799
<211> 405
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 799
atgtacagga tgcagctgct gagctgcatc gccctgagcc tggccctggt gaccaacagc 60

aactgggtga acgtgatctc cgacctgaag aagatcgagg acctgatcca gtccatgcac 120

atcgacgcca ccctgtacac cgagagcgac gtgcacccta gctgcaaggt gaccgccatg 180

aagtgcttcc tgctggagct gcaggtgatc agcctggaga gcggcgatgc cagcatccac 240

gacacagtgg agaacctgat catcctggcc aacaacagcc tgagcagcaa cggcaatgtg 300

accgagagcg gctgcaagga gtgcgaggag ctggaggaga agaacatcaa ggagttcctg 360

cagtccttcg tgcacatcgt gcagatgttc atcaacacca gctaa 405

<210> 800
<211> 912
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 800
atgtacagaa tgcagctgct gagctgcatc gccctgtccc tcgccctggt gaccaactcc 60

gagttctcca ccgagttcat ctccctgatc gccgccctgg ccgtggatta tgtgatcggc 120

atggagaacg ccatgccctg gaatctgccc gccgacctgg cctggttcaa gaggaatacc 180

ctgaacaagc ccgtcatcat gggcaggcac acctgggaaa gcatcggcag acccctgccc 240

ggcaggaaga acatcatcct gtccagccag cccggcaccg acgacagagt gacctgggtg 300

aagagcgtgg acgaagctat cgccgcttgc ggcgacgtgc ccgagatcat ggtgatcggc 360

ggcggcaggg tgatcgaaca gttcctgccc aaggcccaga agctgtacct gacccacatc 420

gatgccgagg tggaaggcga tacacacttc cccgattacg aacctgacga ctgggaaagc 480

gtgttttccg aattccacga cgccgacgcc cagaacagcc acagctactg cttcgagatc 540

ctggaaagaa ggggaggctc cggcggaaac tgggtcaacg tgatcagcga cctgaagaag 600

atcgaggacc tcatccagtc catgcacatt gacgccaccc tgtacaccga gtccgatgtg 660

caccctagct gcaaggtgac cgccatgaaa tgcttcctgc tggagctgca ggtcatctcc 720

ttagaaagcg gcgatgcctc catccacgac accgtggaga acctgatcat cctggccaat 780

aactccctga gcagcaacgg caacgtgacc gagagcggct gcaaagagtg tgaagagctg 840

gaggagaaga acattaagga gttcctgcag agcttcgtgc acatcgtgca aatgttcatc 900

aacaccagct aa 912

<210> 801
<211> 18
<212> PRT
<213> Homo sapiens

<400> 801
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser

<210> 802
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 802
Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln
            20   25

<210> 803
<211> 237
<212> PRT
<213> Homo sapiens

<400> 803
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1   5   10   15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20   25   30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35   40   45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50   55   60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65   70   75   80

Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly
                85   90   95

Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr
            100   105   110

Thr Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro
        115   120   125

Ser Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr
    130   135   140

Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser

145 150 155 160

His Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val
165 170 175

Ala Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser
180 185 190

Leu Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser
195 200 205

Val Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser
210 215 220

Ser Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu
225 230 235

<210> 804
<211> 555
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 804
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

```
Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285
```

```
Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Ile Ser Leu
385                 390                 395                 400

Ile Ala Ala Leu Ala Val Asp His Val Ile Gly Met Glu Asn Ala Met
                405                 410                 415

Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu
            420                 425                 430

Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg
        435                 440                 445

Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr
    450                 455                 460

Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala
465                 470                 475                 480

Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Tyr
                485                 490                 495
```

Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp
500 505 510

Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Lys Pro Asp Asp
515 520 525

Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser
530 535 540

His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
545 550 555

<210> 805
<211> 504
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 805
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys

100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145 150 155 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
165 170 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
180 185 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
195 200 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
210 215 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225 230 235 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
245 250 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
260 265 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
275 280 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
290 295 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln

305 310 315 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
325 330 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
340 345 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
355 360 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
370 375 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Gly Val Gln
385 390 395 400

Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly
405 410 415

Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly Asp Gly Lys Lys
420 425 430

Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly
435 440 445

Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser
450 455 460

Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly
465 470 475 480

Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe
485 490 495

Asp Val Glu Leu Leu Glu Leu Glu
500

<210> 806

<211> 395
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 806

```
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                  10                  15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
            20                  25                  30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175
```

```
Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380
```

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu
385 390 395

<210> 807
<211> 555
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 807
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr

```
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
```

355 360 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
370 375 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Ile Ser Leu
385 390 395 400

Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala Met
405 410 415

Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu
420 425 430

Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg
435 440 445

Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr
450 455 460

Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala
465 470 475 480

Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Ile
485 490 495

Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp
500 505 510

Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp Asp
515 520 525

Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser
530 535 540

His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
545 550 555

<210> 808

<211> 583
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 808

```
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                  10                  15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
            20                  25                  30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175
```

```
Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380
```

```
Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Val Gly Ser
385                 390                 395                 400

Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn
                405                 410                 415

Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln
            420                 425                 430

Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile
        435                 440                 445

Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu
    450                 455                 460

Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro
465                 470                 475                 480

Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu
                485                 490                 495

Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val
            500                 505                 510

Gly Gly Ser Ser Val Ile Lys Glu Phe Met Asn His Pro Gly His Leu
        515                 520                 525

Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe
    530                 535                 540

Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro
545                 550                 555                 560

Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe
                565                 570                 575

Glu Val Tyr Glu Lys Asn Asp
            580
```

<210> 809
<211> 583
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 809
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145 150 155 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser

```
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
```

```
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Val Gly Ser
385                 390                 395                 400

Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn
                405                 410                 415

Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Phe
            420                 425                 430

Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile
        435                 440                 445

Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Phe Arg Pro Leu
    450                 455                 460

Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro
465                 470                 475                 480

Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu
                485                 490                 495

Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val
            500                 505                 510

Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly His Leu
        515                 520                 525

Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe
    530                 535                 540

Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro
545                 550                 555                 560

Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe
                565                 570                 575

Glu Val Tyr Glu Lys Asn Asp
```

580

<210> 810
<211> 54
<212> DNA
<213> Homo sapiens

<400> 810
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagc 54

<210> 811
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 811
tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 60

ggaggaggga gcttgcaa 78

<210> 812
<211> 714
<212> DNA
<213> Homo sapiens

<400> 812
atcacgtgcc ctccccccat gtccgtggaa cacgcagaca tctgggtcaa gagctacagc 60

ttgtactcca gggagcggta catttgtaac tctggtttca agcgtaaagc cggcacgtcc 120

agcctgacgg agtgcgtgtt gaacaaggcc acgaatgtcg cccactggac aacccccagt 180

ctcaaatgca ttagagaccc tgccctggtt caccaaaggc cagcgccacc ctccacagta 240

acgacggcag gggtgacccc acagccagag agcctctccc cttctggaaa agagcccgca 300

gcttcatctc ccagctcaaa caacacagcg gccacaacag cagctattgt cccgggctcc 360

cagctgatgc cttcaaaatc accttccaca ggaaccacag agataagcag tcatgagtcc 420

tcccacggca ccccctctca gacaacagcc aagaactggg aactcacagc atccgcctcc 480

caccagccgc caggtgtgta tccacagggc cacagcgaca ccactgtggc tatctccacg 540

tccactgtcc tgctgtgtgg gctgagcgct gtgtctctcc tggcatgcta cctcaagtca 600

aggcaaactc ccccgctggc cagcgttgaa atggaagcca tggaggctct gccggtgact 660

tgggggacca gcagcagaga tgaagacttg gaaaactgct ctcaccacct atga 714

<210> 813
<211> 711
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 813
attacctgcc cccctccgat gagcgtggag cacgccgaca tctgggtcaa gagctacagc 60

ttgtatagta gggagcggta catctgtaac agcgggttca agaggaaggc cgggaccagc 120

tcactgaccg agtgcgtgtt gaacaaggcc accaacgtgg cccactggac caccctagc 180

cttaagtgca tcagggaccc agcgctcgta caccagagac ccgcgcctcc ctctacggta 240

accacggcag gcgtaacccc ccagcccgag agcctgtccc cgagcggcaa ggagcctgca 300

gcgagcagcc cctcaagcaa caacacagcc gctaccaccg cggcaatcgt gcccggcagc 360

cagctgatgc cctcaaagag ccccagcacc ggcaccactg agataagcag ccacgagagc 420

tcacacggca ctccctcaca gaccactgcc aagaattggg agctgaccgc ctctgccagc 480

caccagcccc caggcgtgta tccccagggc cacagcgaca ccacggtcgc catcagcaca 540

tctacagtgc ttttgtgcgg ccttagcgcc gtgtcactgc tggcatgcta cttgaaaagt 600

aggcaaactc cccctcttgc cagtgtggaa atggaggcca tggaagccct gcccgtgacc 660

tggggcacca gttctaggga cgaggacctt gagaactgct cacatcattt g 711

<210> 814
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 814
atctctctga ttgcggcgct ggcagttgac tacgttattg gcatggaaaa cgcgatgcca 60

tggaacctcc cggctgacct ggcgtggttc aaacgtaaca ccctgaacaa acctgtgatc 120

atgggtcgtc acacctggga atctattggc cgtcctctcc cgggtcgtaa aaacatcatt 180

ctgtcttctc agccaggcac cgacgaccgt gttacctggg ttaaaagcgt tgacgaagcg 240

attgctgcgt gcggtgatgt tcctgaaatt atggtgatcg gcggtggccg tgttatcgaa 300

cagttcctgc cgaaagcgca gaaactgtac ctgacccaca tcgacgcgga agttgaaggt 360

gacacccact tcccggacta cgaaccggat gattgggaga gcgtattctc cgaattccat 420

gatgcggatg cgcaaaactc tcattcttac tgttttgaaa tcctggaacg tcgt 474

<210> 815
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 815
atctctctga ttgcggcgct ggcagttgac cacgttattg gcatggaaaa cgcgatgcca 60

tggaacctcc cggctgacct ggcgtggttc aaacgtaaca ccctgaacaa acctgtgatc 120

atgggtcgtc acacctggga atctattggc cgtcctctcc cgggtcgtaa aaacatcatt 180

ctgtcttctc agccaggcac cgacgaccgt gttacctggg ttaaaagcgt tgacgaagcg 240

attgctgcgt gcggtgatgt tcctgaaatt atggtgatcg gcggtggccg tgtttacgaa 300

cagttcctgc cgaaagcgca gaaactgtac ctgacccaca tcgacgcgga agttgaaggt 360

gacacccact tcccggacta caaaccggat gattgggaga gcgtattctc cgaattccat 420

gatgcggatg cgcaaaactc tcattcttac tgttttgaaa tcctggaacg tcgt 474

<210> 816
<211> 1668
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 816

atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagcgg catctctctg 1200

attgcggcgc tggcagttga ccacgttatt ggcatggaaa acgcgatgcc atggaacctc 1260

ccggctgacc tggcgtggtt caaacgtaac accctgaaca aacctgtgat catgggtcgt 1320

cacacctggg aatctattgg ccgtcctctc ccgggtcgta aaaacatcat tctgtcttct 1380

cagccaggca ccgacgaccg tgttacctgg gttaaaagcg ttgacgaagc gattgctgcg 1440

tgcggtgatg ttcctgaaat tatggtgatc ggcggtggcc gtgtttacga acagttcctg 1500

ccgaaagcgc agaaactgta cctgacccac atcgacgcgg aagttgaagg tgacacccac 1560

ttcccggact acaaaccgga tgattgggag agcgtattct ccgaattcca tgatgcggat 1620

gcgcaaaact ctcattctta ctgttttgaa atcctggaac gtcgttga 1668

<210> 817
<211> 1515
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 817
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagcgg cggcgtgcag 1200

gttgagacta taagcccagg cgacggcagg accttcccca agaggggcca gacatgcgtg 1260

gtgcactaca ccggcatgct tggcgacggc aaaaaggtgg actcaagcag ggacaggaac 1320

aagcccttca agttcatgtt gggcaaacag gaggtgatca gaggctggga ggagggtgtt 1380

gcccagatga gcgtggggca gggcgccaag ctcacgataa gtcccgatta cgcctacggc 1440

gccaccggtc accccggcat catcccccca cacgccaccc tggtgttcga cgtggaattg 1500

ctggagctgg agtga 1515

<210> 818
<211> 1188
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 818
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgtga 1188

<210> 819
<211> 1668
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 819
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagcgg catctctctg 1200

attgcggcgc tggcagttga ctacgttatt ggcatggaaa acgcgatgcc atggaacctc 1260

ccggctgacc tggcgtggtt caaacgtaac accctgaaca aacctgtgat catgggtcgt 1320

cacacctggg aatctattgg ccgtcctctc ccgggtcgta aaaacatcat tctgtcttct 1380

cagccaggca ccgacgaccg tgttacctgg gttaaaagcg ttgacgaagc gattgctgcg 1440

tgcggtgatg ttcctgaaat tatggtgatc ggcggtggcc gtgttatcga acagttcctg 1500

ccgaaagcgc agaaactgta cctgacccac atcgacgcgg aagttgaagg tgacacccac 1560

ttcccggact acgaaccgga tgattgggag agcgtattct ccgaattcca tgatgcggat 1620

gcgcaaaact ctcattctta ctgttttgaa atcctggaac gtcgttga 1668

<210> 820
<211> 1752
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 820
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagcgg cgttggttcg 1200

ctaaactgca tcgtcgctgt gtcccagaac atgggcatcg gcaagaacgg ggacctgccc 1260

tggccaccgc tcaggaatga attcagatat ttccagagaa tgaccacaac ctcttcagta 1320

gaaggtaaac agaatctggt gattatgggt aagaagacct ggttctccat tcctgagaag 1380

aatcgacctt taaagggtag aattaattta gttctcagca gagaactcaa ggaacctcca 1440

caaggagctc attttctttc cagaagtcta gatgatgcct taaaacttac tgaacaacca 1500

gaattagcaa ataaagtaga catggtctgg atagttggtg gcagttctgt tattaaggaa 1560

ttcatgaatc acccaggcca tcttaaacta tttgtgacaa ggatcatgca agactttgaa 1620

agtgacacgt tttttccaga aattgatttg gagaaatata aacttctgcc agaataccca 1680

ggtgttctct ctgatgtcca ggaggagaaa ggcattaagt acaaatttga agtatatgag 1740

aagaatgatt ga 1752

<210> 821
<211> 1752

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 821
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagcgg cgttggttcg 1200

ctaaactgca tcgtcgctgt gtcccagaac atgggcatcg gcaagaacgg ggacctgccc 1260

tggccaccgc tcaggaatga attcagatat ttcttcagaa tgaccacaac ctcttcagta 1320

gaaggtaaac agaatctggt gattatgggt aagaagacct ggttctccat tcctgagaag 1380

ttccgacctt taaagggtag aattaattta gttctcagca gagaactcaa ggaacctcca 1440

caaggagctc attttctttc cagaagtcta gatgatgcct taaaacttac tgaacaacca 1500

gaattagcaa ataaagtaga catggtctgg atagttggtg gcagttctgt tattaaggaa 1560

gccatgaatc acccaggcca tcttaaacta tttgtgacaa ggatcatgca agactttgaa 1620

agtgacacgt tttttccaga aattgatttg gagaaatata aacttctgcc agaataccca 1680

ggtgttctct ctgatgtcca ggaggagaaa ggcattaagt acaaatttga agtatatgag 1740

aagaatgatt ga 1752

<210> 822
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 822
Gly Gly Ser Gly
1

<210> 823
<211> 12
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 823
ggaggatctg ga 12

<210> 824
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 824
Gly Gly Ser Gly Gly Gly
1 5

<210> 825
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 825
ggtggctctg gtggtggt 18

<210> 826
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Linker sequence

<400> 826
ggaggtagtg gtggaggc 18

<210> 827
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 827
Ser Gly Gly Gly Ser
1 5

<210> 828
<211> 15
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 828
tcaggtggcg gtagt 15

<210> 829
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 829
Gly Gly Ser Gly Gly Gly Ser Gly Gly
1 5

<210> 830
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 830
ggaggtagtg gtggaggcag tggtgga 27

<210> 831
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 831
Gly Gly Gly Gly Gly
1 5

<210> 832
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 832
Gly Gly Gly Gly Ser
1 5

<210> 833
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 833
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 834
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 834
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> 835
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 835

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 836
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 836
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 837
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 837
Ser Ser Ser Ser Gly
1 5

<210> 838
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker sequence

<400> 838
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly
1 5 10

<210> 839
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 839
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly
1 5 10 15

<210> 840
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 840
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser
1 5 10 15

Ser Ser Ser Gly
20

<210> 841
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 841
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser
1 5 10 15

Ser Ser Ser Gly Ser Ser Ser Ser Gly
20 25

<210> 842
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 842
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser
1 5 10 15

Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly
20 25 30

<210> 843

<400> 843
000

<210> 844
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 844
agcggcggtg gcagc 15

<210> 845
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 845
Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
1 5 10

<210> 846

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 846
Gly Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Lys Gly
1 5 10 15

<210> 847
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 847
Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Ser Glu Gly Ser Gly Ser
1 5 10 15

Thr Lys Gly

<210> 848
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 848
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

<210> 849
<211> 13
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 849
Val Asp Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Leu Asp
1 5 10

<210> 850
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 850
gtcgactatc cctacgatgt tccggactac gcactggac 39

<210> 851
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 851
Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Glu Phe
1 5 10

<210> 852
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 852
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattacgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aatcatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 853
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 853
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

acggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 854
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 854
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaata acgttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 855
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 855
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tatttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gttattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 856
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 856
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtg cagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacgc gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 857
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 857
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gctattaagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 858
<211> 557
<212> PRT
<213> Homo sapiens

<400> 858
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1 5 10 15

Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
20 25 30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
35 40 45

Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
50 55 60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65 70 75 80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
85 90 95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
100 105 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
115 120 125

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Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205

Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
    210                 215                 220

Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225                 230                 235                 240

Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255

Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270

Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285

Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300

Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320

Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
                325                 330                 335
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Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
            340                 345                 350

Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
        355                 360                 365

Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
    370                 375                 380

Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385                 390                 395                 400

Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
                405                 410                 415

Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
            420                 425                 430

Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
        435                 440                 445

Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
    450                 455                 460

Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465                 470                 475                 480

Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Ala
                485                 490                 495

Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro
            500                 505                 510

Gln Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp
        515                 520                 525

Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala
    530                 535                 540
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Trp Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545                 550                 555


<210> 859
<211> 556
<212> PRT
<213> Homo sapiens

<400> 859
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1               5                   10                  15


Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20                  25                  30


Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
        35                  40                  45


Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
    50                  55                  60


Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65                  70                  75                  80


Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
                85                  90                  95


Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110


Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125


Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140


Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160
```

```
Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205

Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
    210                 215                 220

Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225                 230                 235                 240

Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255

Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270

Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285

Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300

Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320

Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
                325                 330                 335

Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
            340                 345                 350

Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
        355                 360                 365
```

```
Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
    370                 375                 380

Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385                 390                 395                 400

Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
                405                 410                 415

Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
            420                 425                 430

Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
        435                 440                 445

Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
    450                 455                 460

Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465                 470                 475                 480

Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Gly
                485                 490                 495

Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro Gln
            500                 505                 510

Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp Ala
        515                 520                 525

Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala Trp
    530                 535                 540

Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545                 550                 555
```

<210> 860
<211> 557
<212> PRT
<213> Macaca mulatta

<400> 860
Met Pro Pro Pro Cys Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1   5   10   15

Glu Val Arg Pro Gln Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20   25   30

Asn Ala Val Leu Gln Cys Leu Glu Gly Thr Ser Asp Gly Pro Thr Gln
        35   40   45

Gln Leu Val Trp Cys Arg Asp Ser Pro Phe Glu Pro Phe Leu Asn Leu
    50   55   60

Ser Leu Gly Leu Pro Gly Met Gly Ile Arg Met Gly Pro Leu Gly Ile
65   70   75   80

Trp Leu Leu Ile Phe Asn Val Ser Asn Gln Thr Gly Gly Phe Tyr Leu
                85   90   95

Cys Gln Pro Gly Leu Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100   105   110

Val Ser Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115   120   125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130   135   140

Ser Ser Pro Ser Gly Lys Leu Asn Ser Ser Gln Leu Tyr Val Trp Ala
145   150   155   160

Lys Asp Arg Pro Glu Met Trp Glu Gly Glu Pro Val Cys Gly Pro Pro
                165   170   175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180   185   190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195   200   205

```
Arg Gly Pro Leu Ser Trp Thr His Val Arg Pro Lys Gly Pro Lys Ser
    210                 215                 220

Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Asp Arg Asp Met
225                 230                 235                 240

Trp Val Val Asp Thr Gly Leu Leu Leu Thr Arg Ala Thr Ala Gln Asp
                245                 250                 255

Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn Trp Thr Lys Ser Phe Tyr
            260                 265                 270

Leu Glu Ile Thr Ala Arg Pro Ala Leu Trp His Trp Leu Leu Arg Ile
        275                 280                 285

Gly Gly Trp Lys Val Pro Ala Val Thr Leu Thr Tyr Leu Ile Phe Cys
    290                 295                 300

Leu Cys Ser Leu Val Gly Ile Leu Gln Leu Gln Arg Ala Leu Val Leu
305                 310                 315                 320

Arg Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys
                325                 330                 335

Val Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val
            340                 345                 350

Leu Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp
        355                 360                 365

Ala Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser
    370                 375                 380

Asp Val Gln Val Asp Gly Ala Val Gly Ser Arg Ser Pro Pro Gly Ala
385                 390                 395                 400

Gly Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu
                405                 410                 415
```

Glu Gly Ser Glu Phe Tyr Glu Asn Asp Ser Asn Phe Gly Gln Asp Gln
420 425 430

Leu Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu
435 440 445

Gly Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn
450 455 460

Glu Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu
465 470 475 480

Ser Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu
485 490 495

Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly Leu Leu Tyr Ala Ala Pro
500 505 510

Gln Leu Arg Thr Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp
515 520 525

Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala
530 535 540

Trp Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Ala Arg
545 550 555

<210> 861
<211> 557
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 mutant

<400> 861
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1 5 10 15

```
Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20                  25                  30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
        35                  40                  45

Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
    50                  55                  60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65                  70                  75                  80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
                85                  90                  95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205

Arg Gly Pro Leu Ser Trp Thr His Val Arg Pro Lys Gly Pro Lys Ser
    210                 215                 220
```

```
Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Asp Arg Asp Met Trp
225                 230                 235                 240


Val Val Asp Thr Gly Leu Leu Leu Thr Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255


Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270


Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285


Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300


Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320


Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
                325                 330                 335


Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
            340                 345                 350


Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
        355                 360                 365


Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
    370                 375                 380


Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385                 390                 395                 400


Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
                405                 410                 415


Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
            420                 425                 430
```

Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
435 440 445

Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
450 455 460

Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465 470 475 480

Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Ala
485 490 495

Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro
500 505 510

Gln Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp
515 520 525

Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala
530 535 540

Trp Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545 550 555

<210> 862
<211> 557
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 mutant

<400> 862
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1 5 10 15

Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
20 25 30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
35 40 45

```
Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
    50                  55                  60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65                  70                  75                  80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
                85                  90                  95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205

Arg Gly Pro Leu Ser Trp Thr His Val Arg Pro Lys Gly Pro Lys Ser
    210                 215                 220

Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Asp Arg Asp Met Trp
225                 230                 235                 240

Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255
```

```
Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270

Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285

Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300

Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320

Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
                325                 330                 335

Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
            340                 345                 350

Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
        355                 360                 365

Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
    370                 375                 380

Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385                 390                 395                 400

Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
                405                 410                 415

Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
            420                 425                 430

Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
        435                 440                 445

Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
    450                 455                 460
```

```
Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465                 470                 475                 480


Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Ala
                485                 490                 495


Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro
            500                 505                 510


Gln Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp
        515                 520                 525


Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala
    530                 535                 540


Trp Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545                 550                 555


<210> 863
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      CD19 mutant

<400> 863
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1               5                   10                  15


Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Gly Glu Leu
            20                  25                  30


Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu Gly Cys Gly Leu Lys
        35                  40                  45


Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly Lys Leu Met Ser
    50                  55                  60
```

```
Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu Ile Trp Glu Gly
65                  70                  75                  80


Glu Pro Pro Cys Leu Pro Pro Arg Asp Ser Leu Asn Gln Ser Leu Ser
                85                  90                  95


Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu Trp Leu Ser Cys Gly
            100                 105                 110


Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu Ser Trp Thr His Val
        115                 120                 125


His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp
    130                 135                 140


Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro
145                 150                 155                 160


Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn
                165                 170                 175


Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro Val Leu Trp
            180                 185                 190


His Trp Leu Leu Arg Thr Gly Gly Trp Lys Val Ser Ala Val Thr Leu
        195                 200                 205


Ala Tyr Leu Ile Phe Cys Leu Cys Ser Leu Val Gly Ile Leu His Leu
    210                 215                 220


Gln Arg Ala Leu Val Leu Arg Arg Lys Arg Lys Arg Met Thr Asp Pro
225                 230                 235                 240


Thr Arg Arg Phe Phe Lys Val Thr Pro Pro Pro Gly Ser Gly Pro Gln
                245                 250                 255


Asn Gln Tyr Gly Asn Val Leu Ser Leu Pro Thr Pro Thr Ser Gly Leu
            260                 265                 270
```

```
Gly Arg Ala Gln Arg Trp Ala Ala Gly Leu Gly Gly Thr Ala Pro Ser
        275                 280                 285

Tyr Gly Asn Pro Ser Ser Asp Val Gln Ala Asp Gly Ala Leu Gly Ser
    290                 295                 300

Arg Ser Pro Pro Gly Val Gly Pro Glu Glu Glu Glu Gly Glu Gly Tyr
305                 310                 315                 320

Glu Glu Pro Asp Ser Glu Glu Asp Ser Glu Phe Tyr Glu Asn Asp Ser
                325                 330                 335

Asn Leu Gly Gln Asp Gln Leu Ser Gln Asp Gly Ser Gly Tyr Glu Asn
            340                 345                 350

Pro Glu Asp Glu Pro Leu Gly Pro Glu Asp Glu Asp Ser Phe Ser Asn
        355                 360                 365

Ala Glu Ser Tyr Glu Asn Glu Asp Glu Glu Leu Thr Gln Pro Val Ala
    370                 375                 380

Arg Thr Met Asp Phe Leu Ser Pro His Gly Ser Ala Trp Asp Pro Ser
385                 390                 395                 400

Arg Glu Ala Thr Ser Leu Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly
                405                 410                 415

Ile Leu Tyr Ala Ala Pro Gln Leu Arg Ser Ile Arg Gly Gln Pro Gly
            420                 425                 430

Pro Asn His Glu Glu Asp Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro
        435                 440                 445

Asp Gly Pro Asp Pro Ala Trp Gly Gly Gly Gly Arg Met Gly Thr Trp
    450                 455                 460

Ser Thr Arg
465
```

<210> 864
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
CD19 mutant

<400> 864

```
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1               5                  10                  15

Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20                  25                  30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
        35                  40                  45

Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
    50                  55                  60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65                  70                  75                  80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
                85                  90                  95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175
```

```
Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190


Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205


Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
    210                 215                 220


Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225                 230                 235                 240


Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255


Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270


Glu Ile Thr Ala Arg Pro
        275


<210> 865
<211> 189
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      CD19 mutant

<400> 865
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1               5                   10                  15


Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Gly Glu Leu
            20                  25                  30


Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu Gly Cys Gly Leu Lys
        35                  40                  45
```

```
Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly Lys Leu Met Ser
    50                  55                  60

Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu Ile Trp Glu Gly
65                  70                  75                  80

Glu Pro Pro Cys Leu Pro Pro Arg Asp Ser Leu Asn Gln Ser Leu Ser
                85                  90                  95

Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu Trp Leu Ser Cys Gly
            100                 105                 110

Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu Ser Trp Thr His Val
        115                 120                 125

His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp
    130                 135                 140

Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro
145                 150                 155                 160

Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn
                165                 170                 175

Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro
            180                 185


<210> 866
<211> 311
<212> PRT
<213> Renilla reniformis

<400> 866
Met Thr Ser Lys Val Tyr Asp Pro Glu Gln Arg Lys Arg Met Ile Thr
1               5                   10                  15

Gly Pro Gln Trp Trp Ala Arg Cys Lys Gln Met Asn Val Leu Asp Ser
            20                  25                  30

Phe Ile Asn Tyr Tyr Asp Ser Glu Lys His Ala Glu Asn Ala Val Ile
        35                  40                  45
```

```
Phe Leu His Gly Asn Ala Ala Ser Ser Tyr Leu Trp Arg His Val Val
    50                  55                  60

Pro His Ile Glu Pro Val Ala Arg Cys Ile Ile Pro Asp Leu Ile Gly
65                  70                  75                  80

Met Gly Lys Ser Gly Lys Ser Gly Asn Gly Ser Tyr Arg Leu Leu Asp
                85                  90                  95

His Tyr Lys Tyr Leu Thr Ala Trp Phe Glu Leu Leu Asn Leu Pro Lys
            100                 105                 110

Lys Ile Ile Phe Val Gly His Asp Trp Gly Ala Cys Leu Ala Phe His
        115                 120                 125

Tyr Ser Tyr Glu His Gln Asp Lys Ile Lys Ala Ile Val His Ala Glu
    130                 135                 140

Ser Val Val Asp Val Ile Glu Ser Trp Asp Glu Trp Pro Asp Ile Glu
145                 150                 155                 160

Glu Asp Ile Ala Leu Ile Lys Ser Glu Glu Gly Glu Lys Met Val Leu
                165                 170                 175

Glu Asn Asn Phe Phe Val Glu Thr Met Leu Pro Ser Lys Ile Met Arg
            180                 185                 190

Lys Leu Glu Pro Glu Glu Phe Ala Ala Tyr Leu Glu Pro Phe Lys Glu
        195                 200                 205

Lys Gly Glu Val Arg Arg Pro Thr Leu Ser Trp Pro Arg Glu Ile Pro
    210                 215                 220

Leu Val Lys Gly Gly Lys Pro Asp Val Val Gln Ile Val Arg Asn Tyr
225                 230                 235                 240

Asn Ala Tyr Leu Arg Ala Ser Asp Asp Leu Pro Lys Met Phe Ile Glu
                245                 250                 255
```

Ser Asp Pro Gly Phe Phe Ser Asn Ala Ile Val Glu Gly Ala Lys Lys
260 265 270

Phe Pro Asn Thr Glu Phe Val Lys Val Lys Gly Leu His Phe Ser Gln
275 280 285

Glu Asp Ala Pro Asp Glu Met Gly Lys Tyr Ile Lys Ser Phe Val Glu
290 295 300

Arg Val Leu Lys Asn Glu Gln
305 310

<210> 867
<211> 936
<212> DNA
<213> Renilla reniformis

<400> 867
atgacttcca aggtgtacga ccccgagcaa cgcaaacgca tgatcactgg gcctcagtgg 60

tgggctcgct gcaagcaaat gaacgtgctg gactccttca tcaactacta tgattccgag 120

aagcacgccg agaacgccgt gatttttctg catggtaacg ctgcctccag ctacctgtgg 180

aggcacgtcg tgcctcacat cgagcccgtg gctagatgca tcatccctga tctgatcgga 240

atgggtaagt ccggcaagag cgggaatggc tcatatcgcc tcctggatca ctacaagtac 300

ctcaccgctt ggttcgagct gctgaacctt ccaaagaaaa tcatctttgt gggccacgac 360

tgggggggctt gtctggcctt tcactactcc tacgagcacc aagacaagat caaggccatc 420

gtccatgctg agagtgtcgt ggacgtgatc gagtcctggg acgagtggcc tgacatcgag 480

gaggatatcg ccctgatcaa gagcgaagag ggcgagaaaa tggtgcttga gaataacttc 540

ttcgtcgaga ccatgctccc aagcaagatc atgcggaaac tggagcctga ggagttcgct 600

gcctacctgg agccattcaa ggagaagggc gaggttagac ggcctaccct ctcctggcct 660

cgcgagatcc ctctcgttaa gggaggcaag cccgacgtcg tccagattgt ccgcaactac 720

aacgcctacc ttcgggccag cgacgatctg cctaagatgt tcatcgagtc cgaccctggg 780

ttcttttcca acgctattgt cgagggagct aagaagttcc ctaacaccga gttcgtgaag 840

gtgaagggcc tccacttcag ccaggaggac gctccagatg aaatgggtaa gtacatcaag 900

agcttcgtgg agcgcgtgct gaagaacgag cagtaa 936

<210> 868
<211> 550
<212> PRT
<213> Photinus pyralis

<400> 868

```
Met Glu Asp Ala Lys Asn Ile Lys Lys Gly Pro Ala Pro Phe Tyr Pro
1               5                  10                  15

Leu Glu Asp Gly Thr Ala Gly Glu Gln Leu His Lys Ala Met Lys Arg
            20                  25                  30

Tyr Ala Leu Val Pro Gly Thr Ile Ala Phe Thr Asp Ala His Ile Glu
        35                  40                  45

Val Asp Ile Thr Tyr Ala Glu Tyr Phe Glu Met Ser Val Arg Leu Ala
    50                  55                  60

Glu Ala Met Lys Arg Tyr Gly Leu Asn Thr Asn His Arg Ile Val Val
65                  70                  75                  80

Cys Ser Glu Asn Ser Leu Gln Phe Phe Met Pro Val Leu Gly Ala Leu
                85                  90                  95

Phe Ile Gly Val Ala Val Ala Pro Ala Asn Asp Ile Tyr Asn Glu Arg
            100                 105                 110

Glu Leu Leu Asn Ser Met Gly Ile Ser Gln Pro Thr Val Val Phe Val
        115                 120                 125

Ser Lys Lys Gly Leu Gln Lys Ile Leu Asn Val Gln Lys Lys Leu Pro
    130                 135                 140

Ile Ile Gln Lys Ile Ile Ile Met Asp Ser Lys Thr Asp Tyr Gln Gly
145                 150                 155                 160

Phe Gln Ser Met Tyr Thr Phe Val Thr Ser His Leu Pro Pro Gly Phe
```

```
                165                 170                 175

Asn Glu Tyr Asp Phe Val Pro Glu Ser Phe Asp Arg Asp Lys Thr Ile
            180                 185                 190

Ala Leu Ile Met Asn Ser Ser Gly Ser Thr Gly Leu Pro Lys Gly Val
        195                 200                 205

Ala Leu Pro His Arg Thr Ala Cys Val Arg Phe Ser His Ala Arg Asp
    210                 215                 220

Pro Ile Phe Gly Asn Gln Ile Ile Pro Asp Thr Ala Ile Leu Ser Val
225                 230                 235                 240

Val Pro Phe His His Gly Phe Gly Met Phe Thr Thr Leu Gly Tyr Leu
                245                 250                 255

Ile Cys Gly Phe Arg Val Val Leu Met Tyr Arg Phe Glu Glu Glu Leu
            260                 265                 270

Phe Leu Arg Ser Leu Gln Asp Tyr Lys Ile Gln Ser Ala Leu Leu Val
        275                 280                 285

Pro Thr Leu Phe Ser Phe Phe Ala Lys Ser Thr Leu Ile Asp Lys Tyr
    290                 295                 300

Asp Leu Ser Asn Leu His Glu Ile Ala Ser Gly Gly Ala Pro Leu Ser
305                 310                 315                 320

Lys Glu Val Gly Glu Ala Val Ala Lys Arg Phe His Leu Pro Gly Ile
                325                 330                 335

Arg Gln Gly Tyr Gly Leu Thr Glu Thr Thr Ser Ala Ile Leu Ile Thr
            340                 345                 350

Pro Glu Gly Asp Asp Lys Pro Gly Ala Val Gly Lys Val Val Pro Phe
        355                 360                 365

Phe Glu Ala Lys Val Val Asp Leu Asp Thr Gly Lys Thr Leu Gly Val
```

370 375 380

Asn Gln Arg Gly Glu Leu Cys Val Arg Gly Pro Met Ile Met Ser Gly
385 390 395 400

Tyr Val Asn Asn Pro Glu Ala Thr Asn Ala Leu Ile Asp Lys Asp Gly
405 410 415

Trp Leu His Ser Gly Asp Ile Ala Tyr Trp Asp Glu Asp Glu His Phe
420 425 430

Phe Ile Val Asp Arg Leu Lys Ser Leu Ile Lys Tyr Lys Gly Tyr Gln
435 440 445

Val Ala Pro Ala Glu Leu Glu Ser Ile Leu Leu Gln His Pro Asn Ile
450 455 460

Phe Asp Ala Gly Val Ala Gly Leu Pro Asp Asp Asp Ala Gly Glu Leu
465 470 475 480

Pro Ala Ala Val Val Val Leu Glu His Gly Lys Thr Met Thr Glu Lys
485 490 495

Glu Ile Val Asp Tyr Val Ala Ser Gln Val Thr Thr Ala Lys Lys Leu
500 505 510

Arg Gly Gly Val Val Phe Val Asp Glu Val Pro Lys Gly Leu Thr Gly
515 520 525

Lys Leu Asp Ala Arg Lys Ile Arg Glu Ile Leu Ile Lys Ala Lys Lys
530 535 540

Gly Gly Lys Ser Lys Leu
545 550

<210> 869
<211> 1653
<212> DNA
<213> Photinus pyralis

<400> 869

atggaagatg ccaaaaacat taagaagggc ccagcgccat tctacccact cgaagacggg 60

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gcctttaccg acgcacatat cgaggtggac attacctacg ccgagtactt cgagatgagc 180

gttcggctgg cagaagctat gaagcgctat gggctgaata caaaccatcg gatcgtggtg 240

tgcagcgaga atagcttgca gttcttcatg cccgtgttgg gtgccctgtt catcggtgtg 300

gctgtggccc cagctaacga catctacaac gagcgcgagc tgctgaacag catgggcatc 360

agccagccca ccgtcgtatt cgtgagcaag aaagggctgc aaaagatcct caacgtgcaa 420

aagaagctac cgatcataca aaagatcatc atcatggata gcaagaccga ctaccagggc 480

ttccaaagca tgtacacctt cgtgacttcc catttgccac ccggcttcaa cgagtacgac 540

ttcgtgcccg agagcttcga ccgggacaaa accatcgccc tgatcatgaa cagtagtggc 600

agtaccggat tgcccaaggg cgtagcccta ccgcaccgca ccgcttgtgt ccgattcagt 660

catgcccgcg accccatctt cggcaaccag atcatccccg acaccgctat cctcagcgtg 720

gtgccatttc accacggctt cggcatgttc accacgctgg gctacttgat ctgcggcttt 780

cgggtcgtgc tcatgtaccg cttcgaggag gagctattct tgcgcagctt gcaagactat 840

aagattcaat ctgccctgct ggtgcccaca ctatttagct tcttcgctaa gagcactctc 900

atcgacaagt acgacctaag caacttgcac gagatcgcca gcggcggggc gccgctcagc 960

aaggaggtag gtgaggccgt ggccaaacgc ttccacctac caggcatccg ccagggctac 1020

ggcctgacag aaacaaccag cgccattctg atcacccccg aaggggacga caagcctggc 1080

gcagtaggca aggtggtgcc cttcttcgag gctaaggtgg tggacttgga caccggtaag 1140

acactgggtg tgaaccagcg cggcgagctg tgcgtccgtg gccccatgat catgagcggc 1200

tacgttaaca accccgaggc tacaaacgct ctcatcgaca aggacggctg gctgcacagc 1260

ggcgacatcg cctactggga cgaggacgag cacttcttca tcgtggaccg gctgaagagc 1320

ctgatcaaat acaagggcta ccaggtagcc ccagccgaac tggagagcat cctgctgcaa 1380

caccccaaca tcttcgacgc cggggtcgcc ggcctgcccg acgacgatgc cggcgagctg 1440

cccgccgcag tcgtcgtgct ggaacacggt aaaaccatga ccgagaagga gatcgtggac 1500

tatgtggcca gccaggttac aaccgccaag aagctgcgcg gtggtgttgt gttcgtggac 1560

gaggtgccta aaggactgac cggcaagttg gacgcccgca agatccgcga gattctcatt 1620

aaggccaaga agggcggcaa gagcaagctg tga 1653

<210> 870
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 870
Met Val Ser Lys Gly Ala Glu Leu Phe Thr Gly Ile Val Pro Ile Leu
1 5 10 15

Ile Glu Leu Asn Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

Leu Ser Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Ile Gln Glu
85 90 95

Arg Thr Ile Phe Phe Glu Asp Asp Gly Asn Tyr Lys Ser Arg Ala Glu
100 105 110

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Thr Gly
115 120 125

Thr Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly Asn Lys Met Glu Tyr
130 135 140

Asn Tyr Asn Ala His Asn Val Tyr Ile Met Thr Asp Lys Ala Lys Asn
145 150 155 160

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Tyr Phe Gly Phe
210 215 220

Val Thr Ala Ala Ala Ile Thr His Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 871
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 871
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

```
Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Lys Pro Thr Gly Arg Ser Gly Leu Ala Asp Lys Val Asp Met
            100                 105                 110

Ala Arg Ile Val Gly Gly Ser Ser Val Cys Lys Glu Ala Ile Arg Tyr
        115                 120                 125

Pro Gly His Pro Lys Leu Pro Val Thr Arg Thr Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Ser Leu Pro Glu Val Ala Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Gly Ala Gln Glu Glu Lys Gly Ala
                165                 170                 175

Arg Tyr Lys Phe Glu Ala Tyr Glu Arg Ser Asp
            180                 185
```

<210> 872
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 872

```
Met Ala Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                   10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Gly Tyr Phe Arg Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45
```

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Pro Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Arg Asn Asp
180 185

<210> 873
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 873
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Ser
1 5 10 15

Val Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Leu Leu Ser Arg Ser Leu Asp Gly
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Glu Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Val Gln Asp Phe Glu
130 135 140

Ser Gly Thr Phe Phe Pro Glu Ile Asp Leu Glu Arg Tyr Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 874
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 874

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Leu Gln Gly Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Ala Arg Pro Ser Glu Gly Gly Ile Asn Leu Val Leu Ser Arg Glu Pro
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Leu Gly Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110

Val Trp Ile Val Asp Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Pro Lys Leu Phe Val Thr Arg Val Ile Gln Gly Phe Glu
    130                 135                 140

Ser Gly Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Gly Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Gly
            180                 185
```

<210> 875
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 875

```
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                  10                  15

Asn Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
                85                  90                  95

Ala Ser Arg Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Thr
            100                 105                 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
        115                 120                 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
    130                 135                 140

Ser Asp Thr Phe Phe Pro Gly Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160

Pro Gly Tyr Pro Gly Val Leu Ser Asp Val Gln Gly Glu Lys Gly Ile
                165                 170                 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 876
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 876
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Gly Ile Met Gln Gly Ser Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Arg Tyr Glu Leu Leu
145 150 155 160

Pro Gly Tyr Pro Gly Ala Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
165 170 175

Glu Cys Lys Phe Glu Val Tyr Glu Glu Ser Asp
180 185

<210> 877
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 877
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Arg Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Arg Pro Thr Gly Gln Pro Glu Leu Ala Asp Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Arg Glu Ala Met Asn Arg
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Gly Phe Glu
130 135 140

```
Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145                 150                 155                 160


Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile
                165                 170                 175


Lys Tyr Lys Leu Glu Val Tyr Glu Glu Asn Asp
            180                 185


<210> 878
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      destabilizing domain (DD)

<400> 878
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Ser Met Gly
1               5                   10                  15


Ile Gly Lys Asn Gly Asp Leu Ser Trp Pro Pro Leu Arg Asn Glu Phe
            20                  25                  30


Arg Tyr Leu Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
        35                  40                  45


Asn Leu Val Ile Thr Gly Lys Glu Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60


Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65                  70                  75                  80


Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Gly Gly Leu Asp Asp
                85                  90                  95


Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
            100                 105                 110
```

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Ser Tyr
115 120 125

Pro Gly His Leu Lys Leu Leu Val Thr Arg Ile Met Gln Asp Ser Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Pro Pro
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Ala Lys Gly Ile
165 170 175

Lys Tyr Lys Leu Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 879
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 879
Met Ala Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Val Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asp Gly Phe
20 25 30

Arg Tyr Phe Arg Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Ser Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Glu Gly Arg Thr Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala Tyr Leu Leu Ser Arg Ser Leu Asp Asp
85 90 95

```
Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asp Glu Ala Gly Met
            100                 105                 110


Val Trp Val Val Gly Gly Ser Ser Val Asp Lys Glu Ala Met Asn His
        115                 120                 125


Pro Gly His Pro Lys Leu Ser Val Thr Arg Ile Val Gln Asp Phe Gly
    130                 135                 140


Ser Asp Ala Phe Phe Pro Glu Ile Asp Leu Glu Lys Cys Lys Leu Leu
145                 150                 155                 160


Pro Glu Tyr Pro Gly Val Leu Ser Asp Ala Gln Glu Glu Arg Gly Ile
                165                 170                 175


Lys Tyr Lys Phe Glu Val Tyr Glu Lys Ser Asp
            180                 185


<210> 880
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      destabilizing domain (DD)

<400> 880
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1               5                   10                  15


Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Pro Arg His Glu Phe
            20                  25                  30


Arg Tyr Phe Gln Arg Val Thr Thr Thr Ser Ser Ala Glu Gly Lys Gln
        35                  40                  45


Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
    50                  55                  60
```

Asn Arg Pro Ser Lys Gly Arg Ile Gly Leu Val Leu Ser Gly Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Thr Leu Arg Leu Thr Glu Gln Pro Glu Leu Thr Asn Arg Val Asn Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Arg Pro Val Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Ala Phe Phe Pro Glu Val Asp Leu Glu Lys Tyr Arg Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Gly Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Phe Glu Ala Tyr Arg Lys Asn Asp
180 185

<210> 881
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 881
Met Val Gly Ser Leu Asn Cys Ile Val Thr Val Ser Arg Ser Met Gly
1 5 10 15

Ile Gly Lys Asp Gly Asp Leu Ser Trp Pro Pro Leu Arg Ser Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Thr Thr Ala Thr Ser Ser Val Glu Gly Arg Gln
35 40 45

Ser Leu Val Ile Met Gly Lys Arg Thr Trp Phe Ser Thr Pro Glu Arg
50 55 60

Asn Arg Pro Leu Arg Gly Arg Ala Asn Leu Val Leu Ser Gly Glu Leu
65 70 75 80

Lys Gly Pro Pro Gln Gly Ala His Leu Leu Ser Arg Ser Leu Asp Gly
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asp Lys Val Asp Val
100 105 110

Val Arg Ile Val Gly Gly Ser Ser Val Asp Glu Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Val Met Arg Gly Phe Glu
130 135 140

Ser Asp Thr Leu Phe Pro Gly Ile Asp Leu Gly Lys Arg Lys Leu Leu
145 150 155 160

Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Arg Glu Glu Lys Gly Ile
165 170 175

Lys Tyr Lys Leu Glu Val Cys Gly Asn Asn
180 185

<210> 882
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 882
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Val
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 883
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 883
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1   5   10   15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20   25   30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35   40   45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50   55   60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65   70   75   80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85   90   95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100   105   110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
        115   120   125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Ile Gln Asp Phe Glu Ser
    130   135   140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145   150   155   160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165   170   175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180   185

<210> 884
<211> 186

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 884

```
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1               5                  10                  15


Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20                  25                  30


Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35                  40                  45


Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50                  55                  60


Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80


Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95


Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110


Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Tyr His Pro
        115                 120                 125


Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
    130                 135                 140


Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160


Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175
```

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 885
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 885
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
115 120 125

Gly Arg Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Gly Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 886
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 886
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Ser Leu Pro Trp Pro Pro Leu Arg Asn Glu Met Ser
20 25 30

Tyr Phe Ser Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Ser
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 887
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 887
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Asp Met Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Ile Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 888
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 888
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Gly Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Phe Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 889
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 889
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Glu Asn Asp
180 185

<210> 890
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 890
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Phe Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 891
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 891
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

```
Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20                  25                  30

Tyr Phe Phe Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35                  40                  45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Phe
    50                  55                  60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
        115                 120                 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
    130                 135                 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 892
<211> 186
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 892

```
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1               5                  10                  15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20                  25                  30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35                  40                  45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50                  55                  60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Tyr His Pro
        115                 120                 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
    130                 135                 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
```

<210> 893
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 893

```
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1               5                  10                  15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20                  25                  30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35                  40                  45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50                  55                  60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
        115                 120                 125

Gly Arg Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Gly Ser
    130                 135                 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175
```

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 894
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 894
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Val
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 895
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 895
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1 5 10 15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
20 25 30

Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
35 40 45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
50 55 60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65 70 75 80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
85 90 95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
100 105 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
115 120 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
130 135 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145 150 155 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
165 170 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 896
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 896
Met Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly
1 5 10 15

Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe
20 25 30

Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln
35 40 45

Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys
50 55 60

Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu
65 70 75 80

Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp
85 90 95

Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met
100 105 110

Val Trp Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His
115 120 125

Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu
130 135 140

Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu
145 150 155 160

Pro Gly Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Phe
165 170 175

Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
180 185

<210> 897
<211> 106
<212> PRT
<213> Homo sapiens

<400> 897
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1 5 10 15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
20 25 30

Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Trp Val Gly Gly Val
35 40 45

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
50 55 60

Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
65 70 75 80

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
85 90 95

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
100 105

<210> 898
<211> 28
<212> PRT
<213> Homo sapiens

<400> 898
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg
20 25

<210> 899
<211> 73
<212> PRT
<213> Homo sapiens

<400> 899
Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
1 5 10 15

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
20 25 30

Trp Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
35 40 45

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
50 55 60

Tyr Cys Asn His Arg Asn Arg Arg Arg
65 70

<210> 900
<211> 23
<212> PRT
<213> Homo sapiens

<400> 900

Leu Gly Leu Leu Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly
1 5 10 15

Val Ala Ile His Leu Cys Cys
20

<210> 901
<211> 27
<212> PRT
<213> Homo sapiens

<400> 901
Ile Leu Leu Ala Gly Leu Val Ala Ala Asp Ala Val Ala Ser Leu Leu
1 5 10 15

Ile Val Gly Ala Val Phe Leu Cys Ala Arg Arg
20 25

<210> 902
<211> 21
<212> PRT
<213> Homo sapiens

<400> 902
Phe Trp Leu Pro Ile Gly Cys Ala Ala Phe Val Val Val Cys Ile Leu
1 5 10 15

Gly Cys Ile Leu Ile
20

<210> 903
<211> 233
<212> PRT
<213> Homo sapiens

<400> 903
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

```
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Lys Lys Asp
225                 230
```

<210> 904
<211> 21

<212> PRT
<213> Homo sapiens

<400> 904
Leu Leu Phe Leu Ile Leu Gly Val Leu Ser Leu Leu Leu Leu Val Thr
1 5 10 15

Gly Ala Phe Gly Phe
20

<210> 905
<211> 21
<212> PRT
<213> Homo sapiens

<400> 905
Val Ala Ala Ile Leu Gly Leu Gly Leu Val Leu Gly Leu Leu Gly Pro
1 5 10 15

Leu Ala Ile Leu Leu
20

<210> 906
<211> 20
<212> PRT
<213> Homo sapiens

<400> 906
Val Gly Trp Gly Gly Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val
1 5 10 15

Leu Ala Val Ile
20

<210> 907
<211> 27
<212> PRT
<213> Homo sapiens

<400> 907
Phe Trp Ala Leu Val Val Val Ala Gly Val Leu Phe Cys Tyr Gly Leu
1 5 10 15

Leu Val Thr Val Ala Leu Cys Val Ile Trp Thr
20 25

<210> 908
<211> 1335
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
promoter

<400> 908
gagtaattca tacaaaagga ctcgcccctg ccttggggaa tcccagggac cgtcgttaaa 60

ctcccactaa cgtagaaccc agagatcgct gcgttcccgc cccctcaccc gcccgctctc 120

gtcatcactg aggtggagaa gagcatgcgt gaggctccgg tgcccgtcag tgggcagagc 180

gcacatcgcc cacagtcccc gagaagttgg ggggaggggt cggcaattga accggtgcct 240

agagaaggtg gcgcggggta aactgggaaa gtgatgtcgt gtactggctc cgccttttc 300

ccgagggtgg gggagaaccg tatataagtg cagtagtcgc cgtgaacgtt ctttttcgca 360

acgggtttgc cgccagaaca caggtaagtg ccgtgtgtgg ttcccgcggg cctggcctct 420

ttacgggtta tggcccttgc gtgccttgaa ttacttccac gcccctggct gcagtacgtg 480

attcttgatc ccgagcttcg ggttggaagt gggtgggaga gttcgaggcc ttgcgcttaa 540

ggagcccctt cgcctcgtgc ttgagttgag gcctggcttg ggcgctgggg ccgccgcgtg 600

cgaatctggt ggcaccttcg cgcctgtctc gctgctttcg ataagtctct agccatttaa 660

aatttttgat gacctgctgc gacgcttttt ttctggcaag atagtcttgt aaatgcgggc 720

caagatctgc acactggtat ttcggttttt ggggccgcgg gcggcgacgg ggcccgtgcg 780

tcccagcgca catgttcggc gaggcggggc ctgcgagcgc ggccaccgag aatcggacgg 840

gggtagtctc aagctggccg gcctgctctg gtgcctggcc tcgcgccgcc gtgtatcgcc 900

ccgccctggg cggcaaggct ggcccggtcg gcaccagttg cgtgagcgga aagatggccg 960

cttcccggcc ctgctgcagg gagctcaaaa tggaggacgc ggcgctcggg agagcgggcg 1020

ggtgagtcac ccacacaaag gaaaagggcc tttccgtcct cagccgtcgc ttcatgtgac 1080

tccacggagt accgggcgcc gtccaggcac ctcgattagt tctcgagctt ttggagtacg 1140

tcgtctttag gttgggggga ggggttttat gcgatggagt ttccccacac tgagtgggtg 1200

gagactgaag ttaggccagc ttggcacttg atgtaattct ccttggaatt tgccctttt 1260

gagtttggat cttggttcat tctcaagcct cagacagtgg ttcaaagttt ttttcttcca 1320

tttcaggtgt cgtga 1335

<210> 909
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 909
tcaggcgggg ggagt 15

<210> 910
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 910
ggaggaggag gatccggagg aggaggatct ggcggcggcg gcagc 45

<210> 911
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 911
ggaggaggag gatccggagg aggaggatct ggcggaggag gcagc 45

<210> 912
<211> 45
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 912
ggaggaggag gaagcggagg aggaggatcc ggcggaggag gctct 45

<210> 913
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 913
ggaggaggag gcagcggagg aggaggttct ggaggaggcg gcagc 45

<210> 914
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 914
ggcggcggcg gctctggagg aggaggcagc ggcggaggag gctcc 45

<210> 915
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 915
ggaggaggag gcagcggcgg aggaggctcc ggcggcggcg gctct 45

<210> 916
<211> 78
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 916
tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 60

ggtggaggca gcttgcaa 78

<210> 917
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 917
tccggtggag gtagcggtgg agggggttct ggtggaggag gttctggagg tggaggttct 60

ggcggtgggt ccttgcaa 78

<210> 918
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 918
tctggcggag gaagcggagg cggaggatct ggtggtggtg gatctggcgg cggtggtagt 60

ggcggaggtt ctctgcaa 78

<210> 919
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 919
tccgggggggg gtagcggggg agggggttcc ggcgggggag ggtctggagg gggaggttcc 60

ggcgggggggt ccttgcaa 78

<210> 920
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 920
tctggcggag gatctggagg aggcggatct ggaggaggag gcagtggagg cggaggatct 60

ggcggaggat ctctgcag 78

<210> 921
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 921
Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Ser

<210> 922
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 922
Ser 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> 923
<211> 102
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      linker sequence

<400> 923
tctggtggcg ggagtggagg aggtgggtcc ggaggggggag ggagcggtgg tggaggttcc 60

ggcgggggggg gtagtggagg cggagggtca ggtgggggca gc   102

<210> 924
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      linker sequence

<400> 924
agtggtggcg ggtccggcgg tggtggtagc gggggtggag gctcaggtgg cggtggcagt 60

<210> 925
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      cleavable peptide

<400> 925
Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
1   5   10   15

Asn Pro Gly Pro
            20

<210> 926

<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
cleavable peptide

<400> 926
ggagctacta acttcagcct gctgaagcag gctggagacg tggaggagaa ccctggacct 60

<210> 927
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
spacer

<400> 927
tctagataat acgactcact agagatcc 28

<210> 928
<211> 16
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
spacer

<400> 928
tatggccaca accatg 16

<210> 929
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
spacer

<400> 929
aatctagata atacgactca ctagagatcc 30

<210> 930

<211> 54
<212> DNA
<213> Homo sapiens

<400> 930
atggactgga cctggattct gtttctggtg gccgctgcca caagagtgca cagc 54

<210> 931
<211> 54
<212> DNA
<213> Homo sapiens

<400> 931
atggattgga cctggattct gtttctggtg gccgctgcca caagagtgca cagc 54

<210> 932
<211> 30
<212> PRT
<213> Homo sapiens

<400> 932
Met Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala
1 5 10 15

Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly
20 25 30

<210> 933
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 933
atggccccgc ggcgggcgcg cggctgccgg accctcggtc tcccggcgct gctactgctg 60

ctgctgctcc ggccgccggc gacgcggggc 90

<210> 934
<211> 561
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 934
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcgt cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 935
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 935
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggtcctcc 180

attcctgaga agaaccgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 936
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 936
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga aggatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 937
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 937
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

agggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 938
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 938
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccaggagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagt aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 939
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

destabilizing domain (DD)

<400> 939
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgta tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tagagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 940
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 940
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcata 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 941
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 941
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg aggagaatga t 561

<210> 942
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 942
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtaattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaggtatatg agaaggatga t 561

<210> 943
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 943
atggttggtt cgctaaaccg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatgcc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 944
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 944
atggttggtt cgctaaactg catcgttgtt gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc ttattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 945
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 945
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcgg tagaaggtaa acagaatctg gtgattatgg gtaagaaggc ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agagctaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 946
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 946
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag gatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttcttag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtt tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc cgtcttaaac tatttgtgac aaggatcatg 420

caagactttg gaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 947
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 947
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat acttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgag aaggatcatg 420

caagaccttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 948
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 948
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gcacaaattt 540

ggagtatatg agaagaatga t 561

<210> 949
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 949
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggagcctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagacttcg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtacatg aggagaatga t 561

<210> 950
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 950
atggttggtt cgctaaactg catcgccgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaaggc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcta gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 951
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 951
atggttggtt cgctaaactg cgtcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttgaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatgcc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 952
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 952
atggttggct cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggactcgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gcttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaatg taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 953
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 953
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcgagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcatcttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtctataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

ggagtatatg agaagaatga t 561

<210> 954
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 954

atggttggtt cgctgaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcctcag tagaaggtaa gcagaatctg gtgattatgc gtaagaagac ctggttctcc 180

attcctgaga agaatagacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc ccattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggttagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcgtg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctgtgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaggtatatg agaagaatga t 561

<210> 955
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 955
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat acttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagtcctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagca gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttatgac gaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgacc tggagaaata taaactcctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattag gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 956
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 956
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acaggatctg gtgattatgg gtaagaagac ctggtcctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tgtttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattggtt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 957
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 957
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

gaggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agagttaatt tagttcttag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttcc 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggcgttct ctctgatgtc caggaggaga aaggcactaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 958
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 958
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc ccattttctc tccagaagtc tggatgatgc cctaaaacct 300

actggacgat caggattagc agataaagta gacatggccc ggatagttgg cggcagctct 360

gtttgtaagg aagccataag gtacccaggc caccctaagc tacctgtgac aaggaccatg 420

caagactttg aaagtgacac gtctcttcca gaagttgcct tggagaagta taagcttctg 480

ccagaatacc caggtgtgct ctctggtgcc caggaggaga agggcgctag gtacaagttt 540

gaagcatacg aaaggagtga t 561

<210> 959
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 959
atggctggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcggat atttccggag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaacct 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga agggcattaa gtacaaattt 540

gaagtatatg agaggaatga t 561

<210> 960
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 960
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgagcgt cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat attttcagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcatcttctt tccagaagtc tagatggtgc cttaaaactt 300

actgagcaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttatgagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcgtg 420

caagactttg agagtggcac gttttttccca gaaattgatt tggagagata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 961

<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 961
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atctccaggg aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga aggctcgacc ttcagagggt ggaattaatt tagttctcag tagagaaccc 240

aaggaacctc cacaaggagc tcatttcctt tccagaagtc tagatgatgc cttaggactt 300

actgaacaac cggaattagc aaataaagta gacatggtct ggatagttga tggcagctct 360

gtttataagg aagccatgaa tcacccaggc caccctaaac tatttgtgac aagggtcata 420

caaggctttg aaagtggcac gttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgacgtc caggaggga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatgg t 561

<210> 962
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 962
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcaa cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tggatgatgc ctcaagactt 300

actgaacaac cagaattagc caataaagta gacacagtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gttttttcca ggaattgatt tggagaaata taaacttctg 480

ccaggatacc caggtgttct ctctgatgtc caggggggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 963
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 963
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac agggatcatg 420

caaggctctg aaagtgacac gttttttcca gaaattgatt tggagagata tgaacttctg 480

ccaggatacc caggtgctct ctctgatgtt caggaggaga aaggcattga gtgcaaattt 540

gaagtatatg aggagagtga c 561

<210> 964
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 964
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagagctc 240

agggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaagacct 300

actggacaac cagaattagc agataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataggg aagccatgaa tcgcccaggc catcttaaac tgtttgtaac aaggatcatg 420

caaggctttg aaagtgacac gttttttcca gaaattgatt tggagaaata taagcttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaactt 540

gaagtgtatg aggagaatga t 561

<210> 965
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 965
atggttggtt cgctaaactg catcgtcgct gtgtcccaga gcatgggcat cggcaagaac 60

ggggacctgt cctggccacc gctcaggaat gaattcagat atctccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattacgg gtaaggagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaatcaatt tagtcctcag cagagagctc 240

aaggaacctc cacaaggagc tcattttctt tccgggggtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgag ttacccaggc catcttaaac tacttgtgac aaggatcatg 420

caagactctg aaagtgacac gttttttcca gaaattgatt tggagaaata taaacctccg 480

ccagaatacc caggtgttct ctctgatgtc caggaggcga aaggcattaa gtacaaactt 540

gaagtatatg agaagaatga t 561

<210> 966
<211> 561

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 966
atggctggtt cgctaaactg catcgtcgct gtgtcccaga atatgggcgt cggcaagaac 60

ggggacctgc cctggccacc gctcagggat ggattcagat atttccggag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggtcctcc 180

attcctgaga agaatcgacc tttagagggt agaactaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc ttatcttctt tccagaagtc tagatgatgc cttaaaactt 300

actgagcagc cagaattagc agatgaagca ggcatggtct gggtagttgg tggcagttct 360

gttgataagg aagccatgaa tcacccaggc catcccaaac tatctgtgac aaggatcgtg 420

caagactttg gaagtgacgc gttttttcca gaaattgatt tggagaaatg caaacttctg 480

ccagaatacc caggtgttct ctctgatgcc caggaggaga gaggcattaa gtacaaattt 540

gaagtatacg agaagagtga c 561

<210> 967
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 967
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gcccaggcat gaattcagat atttccagag agtgaccaca 120

acctcttcag cagaaggtaa acagaatctg gtgattatgg gcaagaagac ctggttctcc 180

atccctgaga agaatcgacc ttcaaagggt agaattggtt tagttctcag cggagaactc 240

aaggaacctc cacagggagc ccactttctc tccaggagtc tagatgatac cttaagactt 300

actgaacaac cagaattaac gaatagagta aacatggtct ggatagttgg tggcagttct 360

gtttataagg aggccatgaa tcacccaggc caccttagac cagttgtgac aaggatcatg 420

caggactttg aaagcgacgc gtttttttcca gaagttgact tggagaaata tagacttcta 480

ccagaatacc caggtgttct ctctgatgtc caggggggaga aaggcattaa gtacaaattt 540

gaagcatata ggaagaatga t 561

<210> 968
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 968
atggttggct cgctaaactg catcgtcact gtgtcccgga gcatgggcat cggcaaggac 60

ggggacctgt cctggccacc gctcaggagt gaattcaggt actttcagag aacgaccgca 120

acctcttcag tagaaggtag acagagtctg gtgatcatgg gcaagaggac ctggttctcc 180

actcctgaga ggaatcgacc cttaaggggt agagctaact tagttctcag cggagagctc 240

aagggacctc cacaaggagc tcatcttctt tccagaagtc tagatggtgc cttaaaactt 300

actgaacagc cagagttagc agataaagta gacgtggtcc ggatagttgg tggcagttct 360

gttgatgagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aagagtcatg 420

cggggctttg aaagtgatac gctttttcca ggaatcgact tggggaaacg taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc cgggaggaga aaggcattaa gtacaaactt 540

gaagtatgtg ggaataat 558

<210> 969
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 969
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcgtcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 970
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 970
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

ggatacccag gtgttctctc tgatgtccag gaggagaaag gctttaagta caaatttgaa 540

gtatatgaga agaatgattg a 561

<210> 971
<211> 561
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 971
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

ggatacccag gtgttctctc tgatgtccag gaggagaaag gctttaagta caaatttgaa 540

gtatatgaga agaatgattg a 561

<210> 972
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 972
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgagg agaatgat 558

<210> 973
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 973
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaat tcatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgattg a 561

<210> 974
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 974
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaat tcatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 975
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 975
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tcttcagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaagt tccgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgattg a 561

<210> 976
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 976
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tcttcagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaagt tccgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

attaaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 977
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 977
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgtatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 978
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 978
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgaatca cccaggcaga cttaaactat ttgtgacaag gatcatgcaa 420

gactttggaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 979
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 979
gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcgtcgg caagaacggg 60

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 120

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 180

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 240

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 300

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 360

tataaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 420

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 480

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 540

gtatatgaga agaatgat 558

<210> 980
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 980
atggttggtt cgctaaactg catcgtcgct gtgtcccaga acatgggcat cggcaagaac 60

ggggacctgc cctggccacc gctcaggaat gaattcagat atttccagag aatgaccaca 120

acctcttcag tagaaggtaa acagaatctg gtgattatgg gtaagaagac ctggttctcc 180

attcctgaga agaatcgacc tttaaagggt agaattaatt tagttctcag cagagaactc 240

aaggaacctc cacaaggagc tcattttctt tccagaagtc tagatgatgc cttaaaactt 300

actgaacaac cagaattagc aaataaagta gacatggtct ggatagttgg tggcagttct 360

gtttataagg aagccatgaa tcacccaggc catcttaaac tatttgtgac aaggatcatg 420

caagactttg aaagtgacac gtttttttcca gaaattgatt tggagaaata taaacttctg 480

ccaggatacc caggtgttct ctctgatgtc caggaggaga aaggctttaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 981
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 981

```
Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile
1               5                  10                  15

Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg
            20                  25                  30

Tyr Phe Lys Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn
        35                  40                  45

Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn
    50                  55                  60

Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys
65                  70                  75                  80

Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala
                85                  90                  95

Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val
            100                 105                 110

Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro
        115                 120                 125

Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser
    130                 135                 140

Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro
145                 150                 155                 160

Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys
                165                 170                 175

Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
            180                 185
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<210> 982
<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 982
acaacaaccc cagcacccag acctccaaca cctgcaccaa ccatcgcaag ccagcctctg 60

tccctgaggc ccgaggcatg taggccagca gcaggaggcg ccgtgcacac ccggggcctg 120

gactttgcct gcgatatcta tatctgggca ccactggcag gaacatgtgg cgtgctgctg 180

ctgtccctgg tcatcaccct gtattgc 207

<210> 983
<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 983
accacaaccc cagcaccccg cccaccaaca cctgcaccaa ccatcgcctc ccagccactg 60

tctctgaggc ccgaggcatg taggcctgca gcaggaggcg ccgtgcacac caggggcctg 120

gactttgcct gcgatatcta catctgggca cctctggcag gaacatgtgg cgtgctgctg 180

ctgtccctgg tcatcaccct gtattgc 207

<210> 984
<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 984
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggggcg cagtgcacac gaggggggctg 120

gacttcgcct gtgatatcta catctgggcg cccttggccg ggacttgtgg ggtccttctc 180

ctgtcactgg ttatcaccct ttactgc 207

<210> 985
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 985
aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60

actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120

gaactg 126

<210> 986
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 986
agagtgaagt tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 987
<211> 321
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 987
ggcgtgcagg tggagacaat cagcccaggc gacggacgca cctttccaaa gaggggacag 60

acatgcgtgg tgcactacac cggcatgctg gaggatggca agaaggtgga ctcctctaga 120

gatcggaata agccattcaa gtttatgctg ggcaagcagg aagtgatcag aggctgggag 180

gagggagtgg cacagatgtc tgtgggacag cgggccaagc tgacaatcag ccctgactat 240

gcatacggag caaccggaca cccaggaatc atcccaccac acgccacact ggtgttcgat 300

gtggagctgc tgaagcctga g 321

<210> 988
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 988
atctccctga tcgccgccct ggcagtggac tacgtgatcg gcatggagaa cgccatgccc 60

tggaatctgc ctgccgatct ggcctggttt aagagaaaca cactgaataa gcccgtgatc 120

atgggccggc acacctggga gtctatcggc aggcccctgc ctggcaggaa gaacatcatc 180

ctgtcctctc agcctggcac agacgataga gtgacctggg tgaagagcgt ggacgaggca 240

atcgcagcat gtggcgatgt gcccgagatc atggtcatcg gcggcggcag agtgatcgag 300

cagttcctgc ctaaggccca gaagctgtat ctgacacaca tcgacgccga ggtggagggc 360

gacacccact ttccagatta cgagcccgac gattgggagt ccgtgttctc tgagtttcac 420

gacgccgatg cccagaattc ccactcttat tgcttcgaga tcctggagag gaga 474

<210> 989
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 989
ggagtgcagg tggagacaat ctccccaggc gacggcagaa cctttcccaa gcggggccag 60

acatgcgtgg tgcactatac cggcatgctg gaggatggca agaaggtgga ctcctctaga 120

gatcggaaca agccattcaa gtttatgctg ggcaagcagg aagtgatcag aggctgggag 180

gagggagtgg cacagatgtc tgtgggacag cgggccaagc tgacaatcag cccagactat 240

gcatacggag caaccggaca ccctggaatc atccctccac acgccaccct ggtgttcgat 300

gtggagctgc tgaagcctga g 321

<210> 990
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 990
atctacatct gggcaccact ggcaggaaca tgcggcgtgc tgctgctgtc cctggtcatc 60

accctgtatt gt 72

<210> 991
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 991
atctccctga tcgccgccct ggcagtggac tacgtgatcg gcatggagaa cgccatgccc 60

tggaatctgc ctgccgatct ggcctggttt aagagaaaca cactgaataa gcccgtgatc 120

atgggccggc acacctggga gagcatcggc agacctctgc caggccggaa gaacatcatc 180

ctgtcctctc agcctggcac agacgataga gtgacctggg tgaagtccgt ggacgaggca 240

atcgcagcat gcggcgatgt gcccgagatc atggtcatcg gcggcggcag agtgatcgag 300

cagttcctgc ctaaggccca gaagctgtat ctgacacaca tcgacgccga ggtggagggc 360

gacacccact ttccagatta cgagcccgac gattgggagt ccgtgttctc tgagtttcac 420

gacgccgatg cccagaattc ccactcttat tgtttcgaga tcctggagag aaga 474

<210> 992
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 992
atctacatct gggcacctct ggcaggaaca tgcggcgtgc tgctgctgtc tctggtcatc 60

accctgtatt gt 72

<210> 993
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic destabilizing domain (DD)

<400> 993
atctccctga tcgccgccct ggcagtggac cacgtgatcg gcatggagaa cgccatgcca 60

tggaatctgc ccgccgatct ggcctggttc aagcggaaca ccctgaataa gccagtgatc 120

atgggcagac acacatggga gtctatcggc aggcccctgc ctggacgcaa gaacatcatc 180

ctgagctccc agcccggcac cgacgatagg gtgacatggg tgaagtccgt ggacgaggca 240

atcgcagcat gcggcgatgt gcccgagatc atggtcatcg gcggcggcag agtgtacgag 300

cagttcctgc ctaaggccca gaagctgtat ctgacccaca tcgacgccga ggtggagggc 360

gacacacact ttcctgatta caagccagac gattgggagt ccgtgttctc tgagtttcac 420

gacgccgatg cccagaattc tcacagctat tgttttgaga tcctggagcg gaga 474

<210> 994
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 994
ggagtgcagg tggagacaat cagcccaggc gacggaagga cattcccaaa gaggggacag 60

acctgcgtgg tgcactacac aggcatgctg ggcgatggca agaaggtgga cagctcccgg 120

gatagaaaca agcccttcaa gtttatgctg ggcaagcagg aagtgatcag gggatgggag 180

gagggagtgg cacagatgtc cgtgggacag ggcgccaagc tgaccatctc tcctgactac 240

gcctatggag caacaggaca cccaggaatc atcccacctc acgccaccct ggtgtttgat 300

gtggagctgc tggagctgga g 321

<210> 995
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 995
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttcagaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaaga accgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagg ccatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgat 558

<210> 996
<211> 558
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 996
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttcagaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaaga accgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagt tcatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgat 558

<210> 997
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 997
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttaagaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaaga accgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagg ccatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgat 558

<210> 998
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 998
gtgggctccc tgaactgcat cgtggccgtg agccagaaca tgggcatcgg caagaatggc 60

gacctgcctt ggccacctct gaggaacgag ttcagatact ttttcaggat gaccacaacc 120

agctccgtgg agggcaagca gaacctggtc atcatgggca agaagacatg gttctctatc 180

cccgagaagt tccgccctct gaagggccgg atcaatctgg tgctgagcag agagctgaag 240

gagccaccac agggagcaca cttcctgagc cggagcctgg acgatgccct gaagctgacc 300

gagcagcccg agctggccaa caaggtggac atggtgtgga tcgtgggcgg ctctagcgtg 360

atcaaggagg ccatgaatca cccaggccac ctgaagctgt tcgtgacaag aatcatgcag 420

gactttgagt ccgatacctt ctttcccgag atcgacctgg agaagtacaa gctgctgcct 480

gagtatccag gcgtgctgtc tgatgtgcag gaggagaagg gcatcaagta caagttcgag 540

gtgtatgaga agaatgat 558

<210> 999
<211> 576
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 999
cgcccctctc cctccccccc ccctaacgtt actggccgaa gccgcttgga ataaggccgg 60

tgtgcgtttg tctatatgtt attttccacc atattgccgt cttttggcaa tgtgagggcc 120

cggaaacctg gccctgtctt cttgacgagc attcctaggg gtctttcccc tctcgccaaa 180

ggaatgcaag gtctgttgaa tgtcgtgaag gaagcagttc ctctggaagc ttcttgaaga 240

caaacaacgt ctgtagcgac cctttgcagg cagcggaacc ccccacctgg cgacaggtgc 300

ctctgcggcc aaaagccacg tgtataagat acacctgcaa aggcggcaca accccagtgc 360

cacgttgtga gttggatagt tgtggaaaga gtcaaatggc tctcctcaag cgtattcaac 420

aaggggctga aggatgccca gaaggtaccc cattgtatgg gatctgatct ggggcctcgg 480

tgcacatgct ttacatgtgt ttagtcgagg ttaaaaaaac gtctaggccc cccgaaccac 540

ggggacgtgg ttttcctttg aaaaacacga tgataa 576

<210> 1000
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 1000
gcttgccaca acccacaagg agacgacctt cc 32

<210> 1001
<211> 342
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 1001
aattgggtca acgtgatcag cgacctgaag aagatcgagg acctgatcca gagcatgcac 60

atcgacgcca cactgtacac cgagtccgat gtgcacccta gctgcaaagt gaccgccatg 120

aagtgctttc tgctggaact gcaagtgatc agcctggaaa gcggcgacgc cagcatccac 180

gataccgtgg aaaatctgat catcctggcc aacaacagcc tgagcagcaa cggcaatgtg 240

accgagagcg gctgcaaaga gtgcgaggaa ctggaagaga agaacatcaa agagttcctc 300

cagagcttcg tccacatcgt gcagatgttc atcaacacca gc 342

<210> 1002
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 1002
tctggcggag gaagcggagg cggaggatct ggtggtggtg gatctggcgg cggtggtagt 60

ggcggaggtt ctctgcaa 78

<210> 1003
<211> 711
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
payload

<400> 1003
atcacctgtc ctccacctat gagcgtggaa cacgccgaca tctgggtcaa gagctacagc 60

ctgtacagca gagagcggta catctgcaac agcggcttca agagaaaggc cggcacaagc 120

agcctgaccg agtgtgtgct gaacaaggcc acaaacgtgg cccactggac cacacctagc 180

ctgaagtgca tcagagatcc cgctctggtt caccagaggc ctgctcctcc atctacagtg 240

acaacagctg gcgtgacccc tcagcctgag tctctgtctc catctggaaa agagcctgcc 300

gccagctctc ccagctctaa caatactgct gccaccacag ccgccatcgt gcctggatct 360

cagctgatgc ctagcaagag ccctagcacc ggcacaacag agatcagctc tcacgagtct 420

agccacggca ccccatctca gaccacagcc aagaattggg agctgaccgc ctctgcctct 480

catcagccac ctggtgttta ccctcaaggc cactctgata ccaccgtggc catcagcaca 540

agcacagtgc tgctgtgtgg actgtctgcc gtgtctctgc tggcctgcta cctgaagtct 600

agacagacac ctcctctggc cagcgtggaa atggaagcca tggaagctct gcctgtgaca 660

tggggcacca gcagcagaga tgaggacctc gagaattgca gccaccacct g 711

<210> 1004

<400> 1004
000

<210> 1005
<211> 677
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1005
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser

```
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
```

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        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Gly Ser Gly Gly Val Gly Ser Leu Asn
                485                 490                 495

Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp
            500                 505                 510

Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met
        515                 520                 525

Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly
    530                 535                 540

Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly
545                 550                 555                 560

Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly
```

565 570 575

Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu
580 585 590

Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val Gly Gly
595 600 605

Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly His Leu Lys Leu
610 615 620

Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro
625 630 635 640

Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val
645 650 655

Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val
660 665 670

Tyr Glu Lys Asn Asp
675

<210> 1006
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1006
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255
```

```
Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
```

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg Gly Ser
485

<210> 1007
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1007
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu

```
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
```

340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln
485 490 495

Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Gly Ser
500 505

<210> 1008
<211> 497
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1008

```
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 Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Asp Ile
            20                  25                  30

Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg
        35                  40                  45

Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn
    50                  55                  60

Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr His
65                  70                  75                  80

Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
                85                  90                  95

Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp
            100                 105                 110

Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe
        115                 120                 125

Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser Gly
145                 150                 155                 160

Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val
                165                 170                 175

Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro
            180                 185                 190

Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr
        195                 200                 205
```

```
Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp
    210                 215                 220

Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp
225                 230                 235                 240

Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser
                245                 250                 255

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415
```

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly
485 490 495

Ser

<210> 1009
<211> 502
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1009
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145 150 155 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
195 200 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
210 215 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu

275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg Ser Gly Glu Ser Arg Arg Val Arg Arg Asn

485 490 495

Lys Arg Ser Lys Gly Ser
500

<210> 1010

<400> 1010
000

<210> 1011

<400> 1011
000

<210> 1012
<211> 591
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic payload

<400> 1012
agaaacctgc ctgtcgctac ccccgacccc ggaatgttcc cctgcctgca ccactcccag 60

aacctcctga gggccgtgtc caacatgctg cagaaggcta gacagaccct cgaattctac 120

ccctgtacca gcgaggagat cgaccatgag gacatcacca aggataagac cagcaccgtg 180

gaggcttgcc tgcctctgga gctgaccaaa aacgagagct gcctgaacag cagggaaacc 240

agcttcatta ccaacggctc ctgcctggcc tccaggaaga catccttcat gatggccctg 300

tgcctcagca gcatctacga ggacctgaag atgtatcagg tggagtttaa gaccatgaat 360

gccaagctgc tgatggaccc taagaggcag atcttcctgg accagaatat gctggccgtg 420

attgacgagc tgatgcaggc cctcaacttt aacagcgaga ccgtgcccca gaaaagcagc 480

ctcgaagagc ctgacttcta caaaaccaag attaagctgt gtatcctgct gcacgccttc 540

aggatcaggg ccgtgaccat cgacagggtg atgagctacc tgaacgccag t 591

<210> 1013
<211> 321

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 1013
ggagtgcagg tggagacaat cagccccggc gatggcagga cctttcctaa gcgcggccag 60

acatgcgtgg tgcactacac cggcatgctg ggcgacggca agaaggtgga cagctcccgg 120

gatagaaata agcccttcaa gtttatgctg ggcaagcagg aagtgatcag aggctgggag 180

gagggagtgg cacagatgtc tgtgggacag ggcgccaagc tgacaatcag cccagattac 240

gcatatggag caaccggaca cccaggaatc atcccacccc acgccaccct ggtgttcgac 300

gtggagctgc tggagctgga g 321

<210> 1014

<400> 1014
000

<210> 1015
<211> 743
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 1015
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480
```

```
Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu
                485                 490                 495

Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Leu Ser Lys Gly
            500                 505                 510

Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met Arg Phe Lys Val
        515                 520                 525

His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu Ile Glu Gly Glu
    530                 535                 540

Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala Lys Leu Lys Val
545                 550                 555                 560

Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile Leu Ser Pro Gln
                565                 570                 575

Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro Ala Asp Ile Pro
            580                 585                 590

Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys Trp Glu Arg Val
        595                 600                 605

Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr Gln Asp Ser Ser
    610                 615                 620

Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu Arg Gly Thr Asn
625                 630                 635                 640

Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr Met Gly Trp Glu
                645                 650                 655

Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala Leu Lys Gly Glu
            660                 665                 670

Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His Tyr Asp Ala Glu
        675                 680                 685
```

Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln Leu Pro Gly Ala
690 695 700

Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His Asn Glu Asp Tyr
705 710 715 720

Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg His Ser Thr Gly
725 730 735

Gly Met Asp Glu Leu Tyr Lys
740

<210> 1016
<211> 885
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1016
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
```

```
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu
                485                 490                 495

Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Asn Trp Val Asn
            500                 505                 510

Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His
```

```
        515                 520                 525

Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys
    530                 535                 540

Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu
545                 550                 555                 560

Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile
                565                 570                 575

Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly
            580                 585                 590

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu
        595                 600                 605

Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly
    610                 615                 620

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr Cys Pro Pro Pro Met Ser
                645                 650                 655

Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg
            660                 665                 670

Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser
        675                 680                 685

Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp
    690                 695                 700

Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val His Gln
705                 710                 715                 720

Arg Pro Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr Pro Gln
```

725 730 735

Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro
740 745 750

Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro Gly Ser
755 760 765

Gln Leu Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser
770 775 780

Ser His Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn
785 790 795 800

Trp Glu Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val Tyr Pro
805 810 815

Gln Gly His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr Val Leu
820 825 830

Leu Cys Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu Lys Ser
835 840 845

Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala
850 855 860

Leu Pro Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn
865 870 875 880

Cys Ser His His Leu
885

<210> 1017
<211> 907
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 1017

```
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205
```

```
Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415
```

```
Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu
                485                 490                 495

Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Leu Leu Leu
            500                 505                 510

Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe Leu Leu
        515                 520                 525

Ile Pro Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
    530                 535                 540

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
545                 550                 555                 560

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
                565                 570                 575

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
            580                 585                 590

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
        595                 600                 605

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
    610                 615                 620
```

```
Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
625                 630                 635                 640

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
                645                 650                 655

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
            660                 665                 670

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
        675                 680                 685

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
    690                 695                 700

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
705                 710                 715                 720

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
                725                 730                 735

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
            740                 745                 750

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
        755                 760                 765

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
    770                 775                 780

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
785                 790                 795                 800

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
                805                 810                 815

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
            820                 825                 830
```

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
835 840 845

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
850 855 860

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
865 870 875 880

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
885 890 895

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu
900 905

<210> 1018
<211> 903
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 1018
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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
```

290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu
485 490 495

Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Asp Trp Thr

```
            500                 505                 510

Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val His Ser Asn Trp
        515                 520                 525

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
    530                 535                 540

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
545                 550                 555                 560

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
                565                 570                 575

Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
            580                 585                 590

Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
        595                 600                 605

Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
    610                 615                 620

Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
625                 630                 635                 640

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                645                 650                 655

Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr Cys Pro Pro Pro
            660                 665                 670

Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr
        675                 680                 685

Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly
    690                 695                 700

Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala
```

705 710 715 720

His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val
725 730 735

His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr
740 745 750

Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser
755 760 765

Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro
770 775 780

Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu
785 790 795 800

Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala
805 810 815

Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val
820 825 830

Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr
835 840 845

Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu
850 855 860

Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met
865 870 875 880

Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu
885 890 895

Glu Asn Cys Ser His His Leu
900

<210> 1019

<400> 1019
000

<210> 1020

<400> 1020
000

<210> 1021

<400> 1021
000

<210> 1022
<211> 2034
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1022
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg aggcagcgga ggagtgggct ccctgaactg catcgtggcc 1500

gtgagccaga acatgggcat cggcaagaat ggcgacctgc cttggccacc tctgaggaac 1560

gagttcagat actttcagag gatgaccaca accagctccg tggagggcaa gcagaacctg 1620

gtcatcatgg gcaagaagac atggttctct atccccgaga agaaccgccc tctgaagggc 1680

cggatcaatc tggtgctgag cagagagctg aaggagccac cacagggagc acacttcctg 1740

agccggagcc tggacgatgc cctgaagctg accgagcagc ccgagctggc caacaaggtg 1800

gacatggtgt ggatcgtggg cggctctagc gtgatcaagg aggccatgaa tcacccaggc 1860

cacctgaagc tgttcgtgac aagaatcatg caggactttg agtccgatac cttctttccc 1920

gagatcgacc tggagaagta caagctgctg cctgagtatc caggcgtgct gtctgatgtg 1980

caggaggaga agggcatcaa gtacaagttc gaggtgtatg agaagaatga ttga 2034

<210> 1023
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1023

atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg atcctga 1467

<210> 1024

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 1024
Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
1 5

<210> 1025
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 1025
tacccatacg atgttccaga ttacgct 27

<210> 1026
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 1026
tatccttacg atgtgcccga ctatgct 27

<210> 1027
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 1027
tatccgtacg acgtaccaga ctacgca 27

<210> 1028
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
destabilizing domain (DD)

<400> 1028
ggagtgcagg tggaaaccat ctccccagga gacgggcgca ccttccccaa gcgcggccag 60

acctgcgtgg tgcactacac cgggatgctt ggagatggaa agaaagttga ctcctcccgg 120

gacagaaaca agcccтttaa gtttatgcta ggcaagcagg aggtgatccg aggctgggaa 180

gaaggggttg cccagatgag tgtgggtcag ggagccaaac tgactatatc tccagattat 240

gcctatggtg ccactgggca cccaggcatc atcccaccac atgccactct cgtcttcgat 300

gtggagcttc tagaactgga a 321

<210> 1029
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 1029
Leu Ser Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met
1 5 10 15

Arg Phe Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu
20 25 30

Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala
35 40 45

Lys Leu Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile
50 55 60

Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro
65 70 75 80

Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys
85 90 95

Trp Glu Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr
100 105 110

Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu
115 120 125

Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr
130 135 140

Met Gly Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala
145 150 155 160

Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His
165 170 175

Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln
180 185 190

Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His
195 200 205

Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg
210 215 220

His Ser Thr Gly Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 1030
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1030
ttgagcaagg gcgaggagga caacatggcc atcatcaagg agttcatgcg cttcaaggtg 60

cacatggagg gctccgtgaa cggccacgag ttcgagatcg agggcgaggg cgagggccgc 120

ccctacgagg gcacccagac cgccaagctg aaggtgacca agggcggccc cctgcccttc 180

gcctgggaca tcctgtcccc tcagttcatg tacggctcca aggcctacgt gaagcacccc 240

gccgacatcc ccgactactt gaagctgtcc ttccccgagg gcttcaagtg ggagcgcgtg 300

atgaacttcg aggacggcgg cgtggtgacc gtgacccagg actcctccct gcaggacggc 360

gagttcatct acaaggtgaa gctgcgcggc accaacttcc cctccgacgg ccccgtaatg 420

cagaagaaga ccatgggctg ggaggcctcc tccgagcgga tgtaccccga ggacggcgcc 480

ctgaagggcg agatcaagca gaggctgaag ctgaaggacg gcggccacta cgacgccgag 540

gtcaagacca cctacaaggc caagaagccc gtgcagctgc ccggcgccta caacgtcaac 600

atcaagctgg acatcacctc ccacaacgag gactacacca tcgtggaaca gtacgagcgc 660

gccgagggcc gccactccac cggcggcatg gacgagctgt acaag 705

<210> 1031
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 1031
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro
20

<210> 1032
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 1032

atgcttctcc tggtgacaag ccttctgctc tgtgagttac cacacccagc attcctcctg 60

atccca 66

<210> 1033
<211> 1527
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1033
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg agctactaac ttcagcctgc tgaagcaggc tggagacgtg 1500

gaggagaacc ctggacctgg atcctga 1527

<210> 1034
<211> 1494
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1034
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

ccctatcctt acgatgtgcc cgactatgct gacatccaga tgacacagac cacaagctcc 120

ctgtccgcct ctctgggcga cagagtgacc atcagctgcc gggcctccca ggatatctct 180

aagtatctga actggtacca gcagaagccc gatggcacag tgaagctgct gatctatcac 240

accagccgcc tgcactccgg agtgccttct aggttcagcg gctccggctc tggcacagac 300

tacagcctga ccatctccaa cctggagcag gaggatatcg ccacctattt ctgccagcag 360

ggcaatacac tgccttacac ctttggcggc ggcacaaagc tggagatcac cggaggagga 420

ggcagcggag gaggaggctc cggcggcggc ggctctgagg tgaagctgca ggagtccgga 480

ccaggcctgg tggcacctag ccagtccctg tctgtgacat gtaccgtgtc cggcgtgtct 540

ctgccagact acggcgtgtc ttggatcagg cagccaccta ggaagggcct ggagtggctg 600

ggcgtgatct ggggcagcga gacaacatac tataattctg ccctgaagag cagactgaca 660

atcatcaagg acaacagcaa gtcccaggtg ttcctgaaga tgaatagcct gcagacagac 720

gataccgcca tctactattg cgccaagcac tactattacg gcggcagcta tgccatggat 780

tactggggcc agggcacatc cgtgaccgtg tctagcacca caaccccagc acctcgccca 840

ccaacaccag caccaaccat cgcatcccag ccactgtctc tgaggcccga ggcatgtagg 900

cctgcagcag gaggcgccgt gcacaccagg ggcctggact ttgcctgcga tatctatatc 960

tgggcaccac tggcaggaac atgtggcgtg ctgctgctgt ccctggtcat caccctgtat 1020

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cagacaaccc aggaggagga cggctgcagc tgtcggttcc cagaggagga ggagggagga 1140

tgtgagctga gggtgaagtt ttctaggagc gccgatgcac cagcatataa gcagggacag 1200

aaccagctgt acaacgagct gaatctgggc aggagagagg agtacgacgt gctggataag 1260

aggaggggaa gggaccccga gatgggaggc aagccaagga gaaagaaccc ccaggagggc 1320

ctgtataatg agctgcagaa ggacaagatg gccgaggcct actccgagat cggcatgaag 1380

ggagagcggc gcaggggcaa gggacacgat ggcctgtatc agggcctgtc tacagccacc 1440

aaggacacct acgatgcact gcacatgcag gccctgcctc caaggggatc ctga 1494

<210> 1035
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1035
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaaggag tggtgagtcc aggagagtgc ggcgcaacaa gaggagcaag 1500

ggatcctga 1509

<210> 1036

<400> 1036
000

<210> 1037
<211> 3158
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1037

atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60

ccggacatcc agatgacaca gactacatcc tccctgtctg cctctctggg agacagagtc 120

accatcagtt gcagggcaag tcaggacatt agtaaatatt taaattggta tcagcagaaa 180

ccagatggaa ctgttaaact cctgatctac catacatcaa gattacactc aggagtccca 240

tcaaggttca gtggcagtgg gtctggaaca gattattctc tcaccattag caacctggag 300

caagaagata ttgccactta cttttgccaa cagggtaata cgcttccgta cacgttcgga 360

gggggggacca agctggagat cacaggtggc ggtggctcgg gcggtggtgg gtcgggtggc 420

ggcggatctg aggtgaaact gcaggagtca ggacctggcc tggtggcgcc ctcacagagc 480

ctgtccgtca catgcactgt ctcaggggtc tcattacccg actatggtgt aagctggatt 540

cgccagcctc cacgaaaggg tctggagtgg ctgggagtaa tatggggtag tgaaaccaca 600

tactataatt cagctctcaa atccagactg accatcatca aggacaactc caagagccaa 660

gttttcttaa aaatgaacag tctgcaaact gatgacacag ccatttacta ctgtgccaaa 720

cattattact acggtggtag ctatgctatg gactactggg gccaaggaac ctcagtcacc 780

gtctcctcaa ccacgacgcc agcgccgcga ccaccaacac cggcgcccac catcgcgtcg 840

cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg cgggggcgc agtgcacacg 900

agggggctgg acttcgcctg tgatatctac atctgggcgc ccttggccgg gacttgtggg 960

gtccttctcc tgtcactggt tatcaccctt tactgcaaac ggggcagaaa gaaactcctg 1020

tatatattca aacaaccatt tatgagacca gtacaaacta ctcaagagga agatggctgt 1080

agctgccgat ttccagaaga agaagaagga ggatgtgaac tgagagtgaa gttcagcagg 1140

agcgcagacg cccccgcgta caagcagggc cagaaccagc tctataacga gctcaatcta 1200

ggacgaagag aggagtacga tgttttggac aagagacgtg gccgggaccc tgagatgggg 1260

ggaaagccga gaaggaagaa ccctcaggaa ggcctgtaca atgaactgca gaaagataag 1320

atggcggagg cctacagtga gattgggatg aaaggcgagc gccggagggg caaggggcac 1380

gatggccttt accagggtct cagtacagcc accaaggaca cctacgacgc ccttcacatg 1440

caggccctgc cccctcgcac gcgttatccg tacgacgtac cagactacgc aggagtgcag 1500

gtggaaacca tctccccagg agacgggcgc accttcccca agcgcggcca gacctgcgtg 1560

gtgcactaca ccgggatgct tggagatgga aagaaagttg actcctcccg ggacagaaac 1620

aagcccttta agtttatgct aggcaagcag gaggtgatcc gaggctggga agaaggggtt 1680

gcccagatga gtgtgggtca gggagccaaa ctgactatat ctccagatta tgcctatggt 1740

gccactgggc acccaggcat catcccacca catgccactc tcgtcttcga tgtggagctt 1800

ctagaactgg aatgaatgca tcgatccgcg gcggccgcta cgtaaattcc gccccccccc 1860

cccctctccc tccccccccc ctaacgttac tggccgaagc cgcttggaat aaggccggtg 1920

tgcgtttgtc tatatgttat tttccaccat attgccgtct tttggcaatg tgagggcccg 1980

gaaacctggc cctgtcttct tgacgagcat tcctaggggt ctttcccctc tcgccaaagg 2040

aatgcaaggt ctgttgaatg tcgtgaagga agcagttcct ctggaagctt cttgaagaca 2100

aacaacgtct gtagcgaccc tttgcaggca gcggaacccc ccacctggcg acaggtgcct 2160

ctgcggccaa aagccacgtg tataagatac acctgcaaag gcggcacaac cccagtgcca 2220

cgttgtgagt tggatagttg tggaaagagt caaatggctc tcctcaagcg tattcaacaa 2280

ggggctgaag gatgcccaga aggtacccca ttgtatggga tctgatctgg ggcctcggtg 2340

cacatgcttt acatgtgttt agtcgaggtt aaaaaaacgt ctaggccccc cgaaccacgg 2400

ggacgtggtt ttcctttgaa aaacacgatg ataatatggc cacaaccatg atgagcaagg 2460

gcgaggagga taacatggcc atcatcaagg agttcatgcg cttcaaggtg cacatggagg 2520

gctccgtgaa cggccacgag ttcgagatcg agggcgaggg cgagggccgc ccctacgagg 2580

gcacccagac cgccaagctg aaggtgacca agggtggccc cctgcccttc gcctgggaca 2640

tcctgtcccc tcagttcatg tacggctcca aggcctacgt gaagcacccc gccgacatcc 2700

ccgactactt gaagctgtcc ttccccgagg gcttcaagtg ggagcgcgtg atgaacttcg 2760

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cctacaaggc caagaagccc gtgcagctgc ccggcgccta caacgtcaac atcaagttgg 3060

acatcacctc ccacaacgag gactacacca tcgtggaaca gtacgaacgc gccgagggcc 3120

gccactccac cggcggcatg gacgagctgt acaagtaa 3158

<210> 1038

<400> 1038
000

<210> 1039
<211> 2232
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1039
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ccggacatcc agatgacaca gactacatcc tccctgtctg cctctctggg agacagagtc 120

accatcagtt gcagggcaag tcaggacatt agtaaatatt taaattggta tcagcagaaa 180

ccagatggaa ctgttaaact cctgatctac catacatcaa gattacactc aggagtccca 240

tcaaggttca gtggcagtgg gtctggaaca gattattctc tcaccattag caacctggag 300

caagaagata ttgccactta cttttgccaa cagggtaata cgcttccgta cacgttcgga 360

gggggacca agctggagat cacaggtggc ggtggctcgg gcggtggtgg gtcgggtggc 420

ggcggatctg aggtgaaact gcaggagtca ggacctggcc tggtggcgcc ctcacagagc 480

ctgtccgtca catgcactgt ctcaggggtc tcattacccg actatggtgt aagctggatt 540

cgccagcctc cacgaaaggg tctggagtgg ctgggagtaa tatggggtag tgaaaccaca 600

tactataatt cagctctcaa atccagactg accatcatca aggacaactc caagagccaa 660

gttttcttaa aaatgaacag tctgcaaact gatgacacag ccatttacta ctgtgccaaa 720

cattattact acggtggtag ctatgctatg gactactggg gccaaggaac ctcagtcacc 780

gtctcctcaa ccacgacgcc agcgccgcga ccaccaacac cggcgcccac catcgcgtcg 840

cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg cgggggcgc agtgcacacg 900

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gtccttctcc tgtcactggt tatcaccctt tactgcaaac ggggcagaaa gaaactcctg 1020

tatatattca aacaaccatt tatgagacca gtacaaacta ctcaagagga agatggctgt 1080

agctgccgat ttccagaaga agaagaagga ggatgtgaac tgagagtgaa gttcagcagg 1140

agcgcagacg cccccgcgta caagcagggc cagaaccagc tctataacga gctcaatcta 1200

ggacgaagag aggagtacga tgttttggac aagagacgtg gccgggaccc tgagatgggg 1260

ggaaagccga gaaggaagaa ccctcaggaa ggcctgtaca atgaactgca gaaagataag 1320

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gacgtggagg agaaccctgg acctttgagc aagggcgagg aggacaacat ggccatcatc 1560

aaggagttca tgcgcttcaa ggtgcacatg gagggctccg tgaacggcca cgagttcgag 1620

atcgagggcg agggcgaggg ccgcccctac gagggcaccc agaccgccaa gctgaaggtg 1680

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caggactcct ccctgcagga cggcgagttc atctacaagg tgaagctgcg cggcaccaac 1920

ttcccctccg acggccccgt aatgcagaag aagaccatgg gctgggaggc ctcctccgag 1980

cggatgtacc ccgaggacgg cgccctgaag ggcgagatca agcagaggct gaagctgaag 2040

gacggcggcc actacgacgc cgaggtcaag accacctaca aggccaagaa gcccgtgcag 2100

ctgcccggcg cctacaacgt caacatcaag ctggacatca cctcccacaa cgaggactac 2160

accatcgtgg aacagtacga gcgcgccgag ggccgccact ccaccggcgg catggacgag 2220

ctgtacaagt aa 2232

<210> 1040
<211> 2658
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1040
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cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

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tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

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cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

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agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg ttcaggagct actaacttca gcctgctgaa gcaggctgga 1500

gacgtggagg agaaccctgg acctaactgg gtgaacgtga tctccgacct gaaaaagatc 1560

gaggatttga tccagagcat gcacattgac gccaccctgt ataccgagtc cgacgtgcac 1620

ccgagttgca aggtgactgc catgaagtgc ttcctgctgg agctgcaagt gatcagcctg 1680

gagagcggcg acgccagcat ccacgacacc gtggaaaacc ttatcattct ggccaacaat 1740

agcctgagca gcaacggcaa cgtgaccgaa agcggatgta aggaatgcga ggaactggaa 1800

gagaagaata tcaaagaatt cctgcaaagc ttcgtgcaca tcgtgcagat gttcatcaac 1860

acttcttcag gtggcggtag tggtggggga ggatctggag gcggaggaag cgggggtgga 1920

ggttcaggag gagggagctt gcaaattacc tgccccctc cgatgagcgt ggagcacgcc 1980

gacatctggg tcaagagcta cagcttgtat agtagggagc ggtacatctg taacagcggg 2040

ttcaagagga aggccgggac cagctcactg accgagtgcg tgttgaacaa ggccaccaac 2100

gtggcccact ggaccacccc tagccttaag tgcatcaggg acccagcgct cgtacaccag 2160

agacccgcgc ctccctctac ggtaaccacg gcaggcgtaa ccccccagcc cgagagcctg 2220

tccccgagcg gcaaggagcc tgcagcgagc agcccctcaa gcaacaacac agccgctacc 2280

accgcggcaa tcgtgcccgg cagccagctg atgccctcaa agagccccag caccggcacc 2340

actgagataa gcagccacga gagctcacac ggcactccct cacagaccac tgccaagaat 2400

tgggagctga ccgcctctgc cagccaccag cccccaggcg tgtatcccca gggccacagc 2460

gacaccacgg tcgccatcag cacatctaca gtgcttttgt gcggccttag cgccgtgtca 2520

ctgctggcat gctacttgaa aagtaggcaa actccccctc ttgccagtgt ggaaatggag 2580

gccatggaag ccctgcccgt gacctggggc accagttcta gggacgagga ccttgagaac 2640

tgctcacatc atttgtga 2658

<210> 1041
<211> 2724
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1041
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

cccgacatcc agatgacaca gaccacaagc tccctgtccg cctctctggg cgacagagtg 120

accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg ttcaggagct actaacttca gcctgctgaa gcaggctgga 1500

gacgtggagg agaaccctgg acctatgctt ctcctggtga caagccttct gctctgtgag 1560

ttaccacacc cagcattcct cctgatccca aactgggtga acgtgatctc cgacctgaaa 1620

aagatcgagg atttgatcca gagcatgcac attgacgcca ccctgtatac cgagtccgac 1680

gtgcacccga gttgcaaggt gactgccatg aagtgcttcc tgctggagct gcaagtgatc 1740

agcctggaga gcggcgacgc cagcatccac gacaccgtgg aaaaccttat cattctggcc 1800

aacaatagcc tgagcagcaa cggcaacgtg accgaaagcg gatgtaagga atgcgaggaa 1860

ctggaagaga agaatatcaa agaattcctg caaagcttcg tgcacatcgt gcagatgttc 1920

atcaacactt cttcaggtgg cggtagtggt gggggaggat ctggaggcgg aggaagcggg 1980

ggtggaggtt caggaggagg gagcttgcaa attacctgcc cccctccgat gagcgtggag 2040

cacgccgaca tctgggtcaa gagctacagc ttgtatagta gggagcggta catctgtaac 2100

agcgggttca agaggaaggc cgggaccagc tcactgaccg agtgcgtgtt gaacaaggcc 2160

accaacgtgg cccactggac cacccctagc cttaagtgca tcagggaccc agcgctcgta 2220

caccagagac ccgcgcctcc ctctacggta accacggcag gcgtaacccc ccagcccgag 2280

agcctgtccc cgagcggcaa ggagcctgca gcgagcagcc cctcaagcaa caacacagcc 2340

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ggcaccactg agataagcag ccacgagagc tcacacggca ctccctcaca gaccactgcc 2460

aagaattggg agctgaccgc ctctgccagc caccagcccc caggcgtgta tccccagggc 2520

cacagcgaca ccacggtcgc catcagcaca tctacagtgc ttttgtgcgg ccttagcgcc 2580

gtgtcactgc tggcatgcta cttgaaaagt aggcaaactc cccctcttgc cagtgtggaa 2640

atggaggcca tggaagccct gcccgtgacc tggggcacca gttctaggga cgaggacctt 2700

gagaactgct cacatcattt gtga 2724

<210> 1042
<211> 2712
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1042
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accatcagct gccgggcctc ccaggatatc tctaagtatc tgaactggta ccagcagaag 180

cccgatggca cagtgaagct gctgatctat cacaccagcc gcctgcactc cggagtgcct 240

tctaggttca gcggctccgg ctctggcaca gactacagcc tgaccatctc caacctggag 300

caggaggata tcgccaccta tttctgccag cagggcaata cactgcctta cacctttggc 360

ggcggcacaa agctggagat caccggagga ggaggcagcg gaggaggagg ctccggcggc 420

ggcggctctg aggtgaagct gcaggagtcc ggaccaggcc tggtggcacc tagccagtcc 480

ctgtctgtga catgtaccgt gtccggcgtg tctctgccag actacggcgt gtcttggatc 540

aggcagccac ctaggaaggg cctggagtgg ctgggcgtga tctggggcag cgagacaaca 600

tactataatt ctgccctgaa gagcagactg acaatcatca aggacaacag caagtcccag 660

gtgttcctga agatgaatag cctgcagaca gacgataccg ccatctacta ttgcgccaag 720

cactactatt acggcggcag ctatgccatg gattactggg gccagggcac atccgtgacc 780

gtgtctagca ccacaacccc agcacctcgc ccaccaacac cagcaccaac catcgcatcc 840

cagccactgt ctctgaggcc cgaggcatgt aggcctgcag caggaggcgc cgtgcacacc 900

aggggcctgg actttgcctg cgatatctat atctgggcac cactggcagg aacatgtggc 960

gtgctgctgc tgtccctggt catcaccctg tattgcaaga gaggccggaa gaagctgctg 1020

tacatcttca agcagccctt catgaggccc gtgcagacaa cccaggagga ggacggctgc 1080

agctgtcggt tcccagagga ggaggaggga ggatgtgagc tgagggtgaa gttttctagg 1140

agcgccgatg caccagcata taagcaggga cagaaccagc tgtacaacga gctgaatctg 1200

ggcaggagag aggagtacga cgtgctggat aagaggaggg gaagggaccc cgagatggga 1260

ggcaagccaa ggagaaagaa cccccaggag ggcctgtata atgagctgca gaaggacaag 1320

atggccgagg cctactccga gatcggcatg aagggagagc ggcgcagggg caagggacac 1380

gatggcctgt atcagggcct gtctacagcc accaaggaca cctacgatgc actgcacatg 1440

caggccctgc ctccaagggg atccggagct actaacttca gcctgctgaa gcaggctgga 1500

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tgcaaagtga ccgccatgaa gtgctttctg ctggaactgc aagtgatcag cctggaaagc 1740

ggcgacgcca gcatccacga taccgtggaa aatctgatca tcctggccaa caacagcctg 1800

agcagcaacg gcaatgtgac cgagagcggc tgcaaagagt gcgaggaact ggaagagaag 1860

aacatcaaag agttcctcca gagcttcgtc cacatcgtgc agatgttcat caacaccagc 1920

tctggcggag gaagcggagg cggaggatct ggtggtggtg gatctggcgg cggtggtagt 1980

ggcggaggtt ctctgcaaat cacctgtcct ccacctatga gcgtggaaca cgccgacatc 2040

tgggtcaaga gctacagcct gtacagcaga gagcggtaca tctgcaacag cggcttcaag 2100

agaaaggccg gcacaagcag cctgaccgag tgtgtgctga acaaggccac aaacgtggcc 2160

cactggacca cacctagcct gaagtgcatc agagatcccg ctctggttca ccagaggcct 2220

gctcctccat ctacagtgac aacagctggc gtgacccctc agcctgagtc tctgtctcca 2280

tctggaaaag agcctgccgc cagctctccc agctctaaca atactgctgc caccacagcc 2340

gccatcgtgc ctggatctca gctgatgcct agcaagagcc ctagcaccgg cacaacagag 2400

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ctgaccgcct ctgcctctca tcagccacct ggtgtttacc ctcaaggcca ctctgatacc 2520

accgtggcca tcagcacaag cacagtgctg ctgtgtggac tgtctgccgt gtctctgctg 2580

gcctgctacc tgaagtctag acagacacct cctctggcca gcgtggaaat ggaagccatg 2640

gaagctctgc ctgtgacatg gggcaccagc agcagagatg aggacctcga gaattgcagc 2700

caccacctgt ag 2712

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<400> 1043
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<210> 1044

<400> 1044
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<400> 1045
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<400> 1048
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<210> 1049

<400> 1049
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<210> 1050

<400> 1050
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<210> 1051

<400> 1051
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<400> 1052
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<210> 1054

<400> 1054
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<210> 1055
<211> 1170
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 1055
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggat ccggagctac taacttcagc 420

ctgctgaagc aggctggaga cgtggaggag aaccctggac ctttgagcaa gggcgaggag 480

gacaacatgg ccatcatcaa ggagttcatg cgcttcaagg tgcacatgga gggctccgtg 540

aacggccacg agttcgagat cgagggcgag ggcgagggcc gcccctacga gggcacccag 600

accgccaagc tgaaggtgac caagggcggc cccctgccct tcgcctggga catcctgtcc 660

cctcagttca tgtacggctc caaggcctac gtgaagcacc ccgccgacat ccccgactac 720

ttgaagctgt ccttccccga gggcttcaag tgggagcgcg tgatgaactt cgaggacggc 780

ggcgtggtga ccgtgaccca ggactcctcc ctgcaggacg gcgagttcat ctacaaggtg 840

aagctgcgcg gcaccaactt cccctccgac ggccccgtaa tgcagaagaa gaccatgggc 900

tgggaggcct cctccgagcg gatgtacccc gaggacggcg ccctgaaggg cgagatcaag 960

cagaggctga agctgaagga cggcggccac tacgacgccg aggtcaagac cacctacaag 1020

gccaagaagc ccgtgcagct gcccggcgcc tacaacgtca acatcaagct ggacatcacc 1080

tcccacaacg aggactacac catcgtggaa cagtacgagc gcgccgaggg ccgccactcc 1140

accggcggca tggacgagct gtacaagtaa 1170

<210> 1056
<211> 1734
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 1056
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggtt ccgttggttc gctaaactgc 420

atcgtcgctg tgtcccagaa catgggcatc ggcaagaacg gggacctgcc ctggccaccg 480

ctcaggaatg aattcagata tttccagaga atgaccacaa cctcttcagt agaaggtaaa 540

cagaatctgg tgattatggg taagaagacc tggttctcca ttcctgagaa gaatcgacct 600

ttaaagggta gaattaattt agttctcagc agagaactca aggaacctcc acaaggagct 660

cattttcttt ccagaagtct agatgatgcc ttaaaactta ctgaacaacc agaattagca 720

aataaagtag acatggtctg gatagttggt ggcagttctg ttattaagga agccatgaat 780

cacccaggcc atcttaaact atttgtgaca aggatcatgc aagactttga aagtgacacg 840

ttttttccag aaattgattt ggagaaatat aaacttctgc cagaataccc aggtgttctc 900

tctgatgtcc aggaggagaa aggcattaag tacaaatttg aagtatatga gaagaatgat 960

ggatccggag ctactaactt cagcctgctg aagcaggctg gagacgtgga ggagaaccct 1020

ggacctttga gcaagggcga ggaggacaac atggccatca tcaaggagtt catgcgcttc 1080

aaggtgcaca tggagggctc cgtgaacggc cacgagttcg agatcgaggg cgagggcgag 1140

ggccgccccт acgagggcac ccagaccgcc aagctgaagg tgaccaaggg cggccccctg 1200

cccttcgcct gggacatcct gtcccctcag ttcatgtacg gctccaaggc ctacgtgaag 1260

caccccgccg acatccccga ctacttgaag ctgtccttcc ccgagggctt caagtgggag 1320

cgcgtgatga acttcgagga cggcggcgtg gtgaccgtga cccaggactc ctccctgcag 1380

gacggcgagt tcatctacaa ggtgaagctg cgcggcacca acttcccctc cgacggcccc 1440

gtaatgcaga agaagaccat gggctgggag gcctcctccg agcggatgta ccccgaggac 1500

ggcgccctga agggcgagat caagcagagg ctgaagctga aggacggcgg ccactacgac 1560

gccgaggtca agaccaccta caaggccaag aagcccgtgc agctgcccgg cgcctacaac 1620

gtcaacatca agctggacat cacctcccac aacgaggact acaccatcgt ggaacagtac 1680

gagcgcgccg agggccgcca ctccaccggc ggcatggacg agctgtacaa gtaa 1734

<210> 1057
<211> 175
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1057
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65 70 75 80

Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly
85 90 95

Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr
100 105 110

Thr Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro
115 120 125

Ser Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr
130 135 140

Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser
145 150 155 160

His Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr
165 170 175

<210> 1058
<211> 525
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1058
attacctgcc cccctccgat gagcgtggag cacgccgaca tctgggtcaa gagctacagc 60

ttgtatagta gggagcggta catctgtaac agcgggttca agaggaaggc cgggaccagc 120

tcactgaccg agtgcgtgtt gaacaaggcc accaacgtgg cccactggac cacccctagc 180

cttaagtgca tcagggaccc agcgctcgta caccagagac ccgcgcctcc ctctacggta 240

accacggcag gcgtaacccc ccagcccgag agcctgtccc cgagcggcaa ggagcctgca 300

gcgagcagcc cctcaagcaa caacacagcc gctaccaccg cggcaatcgt gcccggcagc 360

cagctgatgc cctcaaagag ccccagcacc ggcaccactg agataagcag ccacgagagc 420

tcacacggca ctccctcaca gaccactgcc aagaattggg agctgaccgc ctctgccagc 480

caccagcccc caggcgtgta tccccagggc cacagcgaca ccacg 525

<210> 1059
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1059
Met Ser Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met
1 5 10 15

Arg Phe Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu
20 25 30

Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala
35 40 45

Lys Leu Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile
50 55 60

Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro
65 70 75 80

Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys
85 90 95

Trp Glu Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr
100 105 110

Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu
115 120 125

Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr
130 135 140

Met Gly Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala
145 150 155 160

Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His
165 170 175

Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln
180 185 190

Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His
195 200 205

Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg
210 215 220

His Ser Thr Gly Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 1060
<211> 708
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1060
atgagcaagg gcgaggagga taacatggcc atcatcaagg agttcatgcg cttcaaggtg 60

cacatggagg gctccgtgaa cggccacgag ttcgagatcg agggcgaggg cgagggccgc 120

ccctacgagg gcacccagac cgccaagctg aaggtgacca agggtggccc cctgcccttc 180

gcctgggaca tcctgtcccc tcagttcatg tacggctcca aggcctacgt gaagcacccc 240

gccgacatcc ccgactactt gaagctgtcc ttccccgagg gcttcaagtg ggagcgcgtg 300

atgaacttcg aggacggcgg cgtggtgacc gtgacccagg actcctccct gcaggacggc 360

gagttcatct acaaggtgaa gctgcgcggc accaacttcc cctccgacgg ccccgtaatg 420

cagaagaaga ccatgggctg ggaggcctcc tccgagcgga tgtaccccga ggacggcgcc 480

ctgaagggcg agatcaagca gaggctgaag ctgaaggacg gcggccacta cgacgctgag 540

gtcaagacca cctacaaggc caagaagccc gtgcagctgc ccggcgccta caacgtcaac 600

atcaagttgg acatcacctc ccacaacgag gactacacca tcgtggaaca gtacgaacgc 660

gccgagggcc gccactccac cggcggcatg gacgagctgt acaagtaa 708

<210> 1061
<211> 583
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1061
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145 150 155 160

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Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365
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Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Val Gly Ser
385                 390                 395                 400

Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn
                405                 410                 415

Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln
            420                 425                 430

Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile
        435                 440                 445

Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu
    450                 455                 460

Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro
465                 470                 475                 480

Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu
                485                 490                 495

Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val
            500                 505                 510

Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly His Leu
        515                 520                 525

Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe
    530                 535                 540

Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro
545                 550                 555                 560

Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe
                565                 570                 575
```

Glu Val Tyr Glu Glu Asn Asp
580

<210> 1062
<211> 583
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1062
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr

```
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
```

```
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Val Gly Ser
385                 390                 395                 400

Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn
                405                 410                 415

Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln
            420                 425                 430

Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile
        435                 440                 445

Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu
    450                 455                 460

Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro
465                 470                 475                 480

Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu
                485                 490                 495

Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val
            500                 505                 510

Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly His Leu
        515                 520                 525

Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe
    530                 535                 540

Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Gly Tyr Pro
545                 550                 555                 560

Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Phe Lys Tyr Lys Phe
```

565 570 575

Glu Val Tyr Glu Lys Asn Asp
580

<210> 1063
<211> 583
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1063
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

```
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160


Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175


Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190


Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205


Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220


Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240


Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255


Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270


Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285


Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300


Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320


Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335


Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350
```

```
Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Val Gly Ser
385                 390                 395                 400

Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly Lys Asn
                405                 410                 415

Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr Phe Gln
            420                 425                 430

Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu Val Ile
        435                 440                 445

Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg Pro Leu
    450                 455                 460

Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu Pro Pro
465                 470                 475                 480

Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu Lys Leu
                485                 490                 495

Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp Ile Val
            500                 505                 510

Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Tyr His Pro Gly His Leu
        515                 520                 525

Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp Thr Phe
    530                 535                 540

Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu Tyr Pro
545                 550                 555                 560
```

Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr Lys Phe
565 570 575

Glu Val Tyr Glu Lys Asn Asp
580

<210> 1064
<211> 404
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1064
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Tyr Pro
145 150 155 160

Tyr Asp Val Pro Asp Tyr Ala Ile Thr Cys Pro Pro Pro Met Ser Val
165 170 175

Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu
180 185 190

Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser
195 200 205

Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr
210 215 220

Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val His Gln Arg
225 230 235 240

Pro Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr Pro Gln Pro
245 250 255

Glu Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro Ser
260 265 270

Ser Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro Gly Ser Gln
275 280 285

Leu Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser Ser
290 295 300

His Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn Trp
305 310 315 320

Glu Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val Tyr Pro Gln
325 330 335

Gly His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr Val Leu Leu

340 345 350

Cys Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu Lys Ser Arg
355 360 365

Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala Leu
370 375 380

Pro Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn Cys
385 390 395 400

Ser His His Leu

<210> 1065

<400> 1065
000

<210> 1066
<211> 403
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1066
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr

```
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val Glu
                165                 170                 175

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
            180                 185                 190

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu
        195                 200                 205

Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
    210                 215                 220

Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val His Gln Arg Pro
225                 230                 235                 240

Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr Pro Gln Pro Glu
                245                 250                 255

Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser
            260                 265                 270

Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro Gly Ser Gln Leu
```

275 280 285

Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser Ser His
290 295 300

Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu
305 310 315 320

Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val Tyr Pro Gln Gly
325 330 335

His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr Val Leu Leu Cys
340 345 350

Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu Lys Ser Arg Gln
355 360 365

Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala Leu Pro
370 375 380

Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn Cys Ser
385 390 395 400

His His Leu

<210> 1067
<211> 403
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1067
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

```
Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Tyr Pro Tyr Asp Val Pro Asp Tyr
145                 150                 155                 160

Ala Ser Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val Glu
                165                 170                 175

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
            180                 185                 190

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu
        195                 200                 205

Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
    210                 215                 220

Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val His Gln Arg Pro
225                 230                 235                 240
```

```
Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr Pro Gln Pro Glu
                245                 250                 255

Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser
            260                 265                 270

Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro Gly Ser Gln Leu
        275                 280                 285

Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser Ser His
    290                 295                 300

Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu
305                 310                 315                 320

Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val Tyr Pro Gln Gly
                325                 330                 335

His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr Val Leu Leu Cys
            340                 345                 350

Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu Lys Ser Arg Gln
        355                 360                 365

Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala Leu Pro
    370                 375                 380

Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn Cys Ser
385                 390                 395                 400

His His Leu
```

<210> 1068
<211> 371
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

construct

<400> 1068

```
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                  10                  15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
            20                  25                  30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu
    130                 135                 140

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
145                 150                 155                 160

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu
                165                 170                 175

Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
            180                 185                 190

Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val His Gln Arg Pro
```

195 200 205

Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr Pro Gln Pro Glu
210 215 220

Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser
225 230 235 240

Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro Gly Ser Gln Leu
245 250 255

Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu Ile Ser Ser His
260 265 270

Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu
275 280 285

Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val Tyr Pro Gln Gly
290 295 300

His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr Val Leu Leu Cys
305 310 315 320

Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu Lys Ser Arg Gln
325 330 335

Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met Glu Ala Leu Pro
340 345 350

Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu Glu Asn Cys Ser
355 360 365

His His Leu
370

<210> 1069
<211> 407
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1069

```
Met Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala
1               5                  10                  15

Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Asn Trp
            20                  25                  30

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
        35                  40                  45

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
    50                  55                  60

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
65                  70                  75                  80

Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
                85                  90                  95

Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
            100                 105                 110

Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
        115                 120                 125

Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
145                 150                 155                 160

Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr Cys Pro Pro Pro
                165                 170                 175

Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr
            180                 185                 190
```

```
Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly
        195                 200                 205

Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala
    210                 215                 220

His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp Pro Ala Leu Val
225                 230                 235                 240

His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr Ala Gly Val Thr
                245                 250                 255

Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu Pro Ala Ala Ser
            260                 265                 270

Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala Ala Ile Val Pro
        275                 280                 285

Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr Gly Thr Thr Glu
    290                 295                 300

Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser Gln Thr Thr Ala
305                 310                 315                 320

Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln Pro Pro Gly Val
                325                 330                 335

Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile Ser Thr Ser Thr
            340                 345                 350

Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu Ala Cys Tyr Leu
        355                 360                 365

Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu Met Glu Ala Met
    370                 375                 380

Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg Asp Glu Asp Leu
385                 390                 395                 400
```

Glu Asn Cys Ser His His Leu
405

<210> 1070
<211> 397
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1070
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr

```
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
```

355 360 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
370 375 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser
385 390 395

<210> 1071
<211> 555
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1071
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

```
Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335
```

```
Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Gly Ile Ser Leu
385                 390                 395                 400

Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala Met
                405                 410                 415

Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu
            420                 425                 430

Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg
        435                 440                 445

Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr
    450                 455                 460

Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala
465                 470                 475                 480

Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Ile
                485                 490                 495

Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp
            500                 505                 510

Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp Asp
        515                 520                 525

Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser
    530                 535                 540
```

His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
545 550 555

<210> 1072

<400> 1072
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<210> 1073

<400> 1073
000

<210> 1074
<211> 573
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1074
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
50 55 60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65 70 75 80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
85 90 95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys

100 105 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
115 120 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
165 170 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
180 185 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
195 200 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
210 215 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225 230 235 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
245 250 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
260 265 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
275 280 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
290 295 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro

```
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385                 390                 395                 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Ile
                405                 410                 415

Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn
            420                 425                 430

Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn
        435                 440                 445

Thr Leu Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile
    450                 455                 460

Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro
465                 470                 475                 480

Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile
                485                 490                 495

Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg
            500                 505                 510

Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His
```

515 520 525

Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro
530 535 540

Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln
545 550 555 560

Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
565 570

<210> 1075
<211> 414
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1075
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
50 55 60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65 70 75 80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
85 90 95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
100 105 110

```
Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
        115                 120                 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
                165                 170                 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225                 230                 235                 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
                245                 250                 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
            260                 265                 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320
```

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
325 330 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
340 345 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
355 360 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
370 375 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385 390 395 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser
405 410

<210> 1076
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1076
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
50 55 60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser

65 70 75 80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
85 90 95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
100 105 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
115 120 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
165 170 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
180 185 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
195 200 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
210 215 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225 230 235 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
245 250 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
260 265 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr

```
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385                 390                 395                 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
                405                 410                 415

Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly
            420                 425                 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr
        435                 440                 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
    450                 455                 460

Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465                 470                 475                 480

Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
```

485 490 495

Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
500 505 510

Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
515 520 525

Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly
530 535 540

His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp
545 550 555 560

Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu
565 570 575

Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr
580 585 590

Lys Phe Glu Val Tyr Glu Glu Asn Asp
595 600

<210> 1077
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1077
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

```
Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
    50                  55                  60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65                  70                  75                  80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
                85                  90                  95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
            100                 105                 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
        115                 120                 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
                165                 170                 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225                 230                 235                 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
                245                 250                 255
```

```
Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
            260                 265                 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385                 390                 395                 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
                405                 410                 415

Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly
            420                 425                 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr
        435                 440                 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
    450                 455                 460
```

```
Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465                 470                 475                 480


Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
                485                 490                 495


Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
            500                 505                 510


Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
        515                 520                 525


Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly
    530                 535                 540


His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp
545                 550                 555                 560


Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Gly
                565                 570                 575


Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Phe Lys Tyr
            580                 585                 590


Lys Phe Glu Val Tyr Glu Lys Asn Asp
        595                 600


<210> 1078
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 1078
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                   10                  15


His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
```

```
            20                  25                  30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
        35                  40                  45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
    50                  55                  60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65                  70                  75                  80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
                85                  90                  95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
            100                 105                 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
        115                 120                 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
                165                 170                 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
```

225 230 235 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
245 250 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
260 265 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
275 280 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
290 295 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305 310 315 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
325 330 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
340 345 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
355 360 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
370 375 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385 390 395 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
405 410 415

Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly
420 425 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr

435 440 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
450 455 460

Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465 470 475 480

Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
485 490 495

Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
500 505 510

Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
515 520 525

Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly
530 535 540

Arg Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Gly Ser Asp
545 550 555 560

Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu
565 570 575

Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr
580 585 590

Lys Phe Glu Val Tyr Glu Lys Asn Asp
595 600

<210> 1079
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1079

```
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                  10                  15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
            20                  25                  30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
        35                  40                  45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
    50                  55                  60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65                  70                  75                  80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
                85                  90                  95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
            100                 105                 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
        115                 120                 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
                165                 170                 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205
```

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Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225                 230                 235                 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
                245                 250                 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
            260                 265                 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385                 390                 395                 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
                405                 410                 415
```

```
Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Val Gly
            420                 425                 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr
        435                 440                 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
    450                 455                 460

Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465                 470                 475                 480

Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
                485                 490                 495

Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
            500                 505                 510

Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
        515                 520                 525

Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Asn His Pro Gly
    530                 535                 540

His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp
545                 550                 555                 560

Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu
                565                 570                 575

Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr
            580                 585                 590

Lys Phe Glu Val Tyr Glu Lys Asn Asp
        595                 600
```

<210> 1080
<211> 601
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1080
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
50 55 60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65 70 75 80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
85 90 95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
100 105 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
115 120 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
165 170 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys

```
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225                 230                 235                 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
                245                 250                 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
            260                 265                 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365

Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
```

385 390 395 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
405 410 415

Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Ile Gly
420 425 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr
435 440 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
450 455 460

Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465 470 475 480

Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
485 490 495

Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
500 505 510

Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
515 520 525

Ile Val Gly Gly Ser Ser Val Tyr Lys Glu Ala Met Tyr His Pro Gly
530 535 540

His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp
545 550 555 560

Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu
565 570 575

Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr
580 585 590

Lys Phe Glu Val Tyr Glu Lys Asn Asp

595 600

<210> 1081
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1081
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asp Tyr Lys Asp Asp Asp Asp Lys Asn Trp Val Asn Val Ile
20 25 30

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
35 40 45

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
50 55 60

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser
65 70 75 80

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
85 90 95

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
100 105 110

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
115 120 125

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

```
Gly Gly Gly Ser Leu Gln Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ile
                165                 170                 175

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
            180                 185                 190

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
        195                 200                 205

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
    210                 215                 220

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
225                 230                 235                 240

Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr
                245                 250                 255

Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys
            260                 265                 270

Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr
        275                 280                 285

Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser
    290                 295                 300

Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro
305                 310                 315                 320

Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His
                325                 330                 335

Gln Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala
            340                 345                 350

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
        355                 360                 365
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Leu Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val
    370                 375                 380

Glu Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser
385                 390                 395                 400

Arg Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Val
                405                 410                 415

Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln Asn Met Gly Val Gly
            420                 425                 430

Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg Asn Glu Phe Arg Tyr
        435                 440                 445

Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu Gly Lys Gln Asn Leu
    450                 455                 460

Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile Pro Glu Lys Asn Arg
465                 470                 475                 480

Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser Arg Glu Leu Lys Glu
                485                 490                 495

Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser Leu Asp Asp Ala Leu
            500                 505                 510

Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys Val Asp Met Val Trp
        515                 520                 525

Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala Met Asn His Pro Gly
    530                 535                 540

His Leu Lys Leu Phe Val Thr Arg Ile Met Gln Asp Phe Glu Ser Asp
545                 550                 555                 560

Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr Lys Leu Leu Pro Glu
                565                 570                 575
```

Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu Lys Gly Ile Lys Tyr
580 585 590

Lys Phe Glu Val Tyr Glu Lys Asn Asp
595 600

<210> 1082
<211> 681
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1082
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145 150 155 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
165 170 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
180 185 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
195 200 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
210 215 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225 230 235 240

Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
245 250 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
260 265 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
275 280 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
290 295 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305 310 315 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
325 330 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu

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            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Ser Arg Met Asp Tyr
385                 390                 395                 400

Lys Asp Asp Asp Asp Lys Asp Tyr Lys Asp Asp Asp Asp Lys Asp Tyr
                405                 410                 415

Lys Asp Asp Asp Asp Lys Ser Arg Gly Ser Gly Ala Thr Asn Phe Ser
            420                 425                 430

Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Leu Ser
        435                 440                 445

Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met Arg Phe
    450                 455                 460

Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu Ile Glu
465                 470                 475                 480

Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala Lys Leu
                485                 490                 495

Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile Leu Ser
            500                 505                 510

Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro Ala Asp
        515                 520                 525

Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys Trp Glu
    530                 535                 540

Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr Gln Asp
```

545 550 555 560

Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu Arg Gly
565 570 575

Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr Met Gly
580 585 590

Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala Leu Lys
595 600 605

Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His Tyr Asp
610 615 620

Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln Leu Pro
625 630 635 640

Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His Asn Glu
645 650 655

Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg His Ser
660 665 670

Thr Gly Gly Met Asp Glu Leu Tyr Lys
675 680

<210> 1083
<211> 652
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1083
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

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Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ile Thr
145                 150                 155                 160

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                165                 170                 175

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            180                 185                 190

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        195                 200                 205

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Asp
    210                 215                 220

Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val Thr Thr
225                 230                 235                 240
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Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly Lys Glu
                245                 250                 255

Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr Thr Ala
            260                 265                 270

Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro Ser Thr
        275                 280                 285

Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr Pro Ser
    290                 295                 300

Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser His Gln
305                 310                 315                 320

Pro Pro Gly Val Tyr Pro Gln Gly His Ser Asp Thr Thr Val Ala Ile
                325                 330                 335

Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu Leu
            340                 345                 350

Ala Cys Tyr Leu Lys Ser Arg Gln Thr Pro Pro Leu Ala Ser Val Glu
        355                 360                 365

Met Glu Ala Met Glu Ala Leu Pro Val Thr Trp Gly Thr Ser Ser Arg
    370                 375                 380

Asp Glu Asp Leu Glu Asn Cys Ser His His Leu Gly Ser Gly Ala Thr
385                 390                 395                 400

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
                405                 410                 415

Pro Leu Ser Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe
            420                 425                 430

Met Arg Phe Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe
        435                 440                 445
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Glu Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr
    450                 455                 460

Ala Lys Leu Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp
465                 470                 475                 480

Ile Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His
                485                 490                 495

Pro Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe
            500                 505                 510

Lys Trp Glu Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val
        515                 520                 525

Thr Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys
    530                 535                 540

Leu Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys
545                 550                 555                 560

Thr Met Gly Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly
                565                 570                 575

Ala Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly
            580                 585                 590

His Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val
        595                 600                 605

Gln Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser
    610                 615                 620

His Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly
625                 630                 635                 640

Arg His Ser Thr Gly Gly Met Asp Glu Leu Tyr Lys
                645                 650
```

<210> 1084

<400> 1084
000

<210> 1085

<400> 1085
000

<210> 1086
<211> 1752
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1086
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagtgg tgttggttcg 1200

ctaaactgca tcgtcgctgt gtcccagaac atgggcatcg gcaagaacgg ggacctgccc 1260

tggccaccgc tcaggaatga attcagatat ttccagagaa tgaccacaac ctcttcagta 1320

gaaggtaaac agaatctggt gattatgggt aagaagacct ggttctccat tcctgagaag 1380

aatcgacctt taaagggtag aattaattta gttctcagca gagaactcaa ggaacctcca 1440

caaggagctc attttctttc cagaagtcta gatgatgcct taaaacttac tgaacaacca 1500

gaattagcaa ataaagtaga catggtctgg atagttggtg gcagttctgt ttataaggaa 1560

gccatgaatc acccaggcca tcttaaacta tttgtgacaa ggatcatgca agactttgaa 1620

agtgacacgt tttttccaga aattgatttg gagaaatata aacttctgcc agaataccca 1680

ggtgttctct ctgatgtcca ggaggagaaa ggcattaagt acaaatttga agtatatgag 1740

gagaatgatt ga 1752

<210> 1087
<211> 1752
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1087
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagtgg tgttggttcg 1200

ctaaactgca tcgtcgctgt gtcccagaac atgggcatcg gcaagaacgg ggacctgccc 1260

tggccaccgc tcaggaatga attcagatat ttccagagaa tgaccacaac ctcttcagta 1320

gaaggtaaac agaatctggt gattatgggt aagaagacct ggttctccat tcctgagaag 1380

aatcgacctt taaagggtag aattaattta gttctcagca gagaactcaa ggaacctcca 1440

caaggagctc attttctttc cagaagtcta gatgatgcct taaaacttac tgaacaacca 1500

gaattagcaa ataaagtaga catggtctgg atagttggtg gcagttctgt ttataaggaa 1560

gccatgaatc acccaggcca tcttaaacta tttgtgacaa ggatcatgca agactttgaa 1620

agtgacacgt tttttccaga aattgatttg gagaaatata aacttctgcc aggataccca 1680

ggtgttctct ctgatgtcca ggaggagaaa ggctttaagt acaaatttga agtatatgag 1740

aagaatgatt ga 1752

<210> 1088

<211> 1752
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1088
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgagtgg tgttggttcg 1200

ctaaactgca tcgtcgctgt gtcccagaac atgggcatcg gcaagaacgg ggacctgccc 1260

tggccaccgc tcaggaatga attcagatat ttccagagaa tgaccacaac ctcttcagta 1320

gaaggtaaac agaatctggt gattatgggt aagaagacct ggttctccat tcctgagaag 1380

aatcgacctt taaagggtag aattaattta gttctcagca gagaactcaa ggaacctcca 1440

caaggagctc attttctttc cagaagtcta gatgatgcct taaaacttac tgaacaacca 1500

gaattagcaa ataaagtaga catggtctgg atagttggtg gcagttctgt ttataaggaa 1560

gccatgtatc acccaggcca tcttaaacta tttgtgacaa ggatcatgca agactttgaa 1620

agtgacacgt tttttccaga aattgatttg gagaaatata aacttctgcc agaataccca 1680

ggtgttctct ctgatgtcca ggaggagaaa ggcattaagt acaaatttga agtatatgag 1740

aagaatgatt ga 1752

<210> 1089
<211> 1215
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1089
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtggggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggtg gaggcagctt gcaataccca 480

tacgatgttc cagattacgc tattacctgc ccccctccga tgagcgtgga gcacgccgac 540

atctgggtca agagctacag cttgtatagt agggagcggt acatctgtaa cagcgggttc 600

aagaggaagg ccgggaccag ctcactgacc gagtgcgtgt tgaacaaggc caccaacgtg 660

gcccactgga ccacccctag ccttaagtgc atcagggacc agcgctcgt acaccagaga 720

cccgcgcctc cctctacggt aaccacggca ggcgtaaccc cccagcccga gagcctgtcc 780

ccgagcggca aggagcctgc agcgagcagc ccctcaagca acaacacagc cgctaccacc 840

gcggcaatcg tgcccggcag ccagctgatg ccctcaaaga gccccagcac cggcaccact 900

gagataagca gccacgagag ctcacacggc actccctcac agaccactgc caagaattgg 960

gagctgaccg cctctgccag ccaccagccc ccaggcgtgt atccccaggg ccacagcgac 1020

accacggtcg ccatcagcac atctacagtg cttttgtgcg gccttagcgc cgtgtcactg 1080

ctggcatgct acttgaaaag taggcaaact ccccctcttg ccagtgtgga aatggaggcc 1140

atggaagccc tgcccgtgac ctggggcacc agttctaggg acgaggacct tgagaactgc 1200

tcacatcatt tgtga 1215

<210> 1090

<400> 1090
000

<210> 1091
<211> 1212
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1091
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttctg gtggcgggag tggaggaggt 420

gggtccggag ggggagggag cggtggtgga ggttccggcg gggggggtag tggaggcgga 480

gggtcaggtg ggggcagcat tacctgcccc cctccgatga gcgtggagca cgccgacatc 540

tgggtcaaga gctacagctt gtatagtagg gagcggtaca tctgtaacag cgggttcaag 600

aggaaggccg ggaccagctc actgaccgag tgcgtgttga acaaggccac caacgtggcc 660

cactggacca cccctagcct taagtgcatc agggacccag cgctcgtaca ccagagaccc 720

gcgcctccct ctacggtaac cacggcaggc gtaacccccc agcccgagag cctgtccccg 780

agcggcaagg agcctgcagc gagcagcccc tcaagcaaca acacagccgc taccaccgcg 840

gcaatcgtgc ccggcagcca gctgatgccc tcaaagagcc ccagcaccgg caccactgag 900

ataagcagcc acgagagctc acacggcact ccctcacaga ccactgccaa gaattgggag 960

ctgaccgcct ctgccagcca ccagccccca ggcgtgtatc cccagggcca cagcgacacc 1020

acggtcgcca tcagcacatc tacagtgctt ttgtgcggcc ttagcgccgt gtcactgctg 1080

gcatgctact tgaaaagtag gcaaactccc cctcttgcca gtgtggaaat ggaggccatg 1140

gaagccctgc ccgtgacctg gggcaccagt tctagggacg aggaccttga gaactgctca 1200

catcatttgt ga 1212

<210> 1092
<211> 1212
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1092
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttctagtg gtggcgggtc cggcggtggt 420

ggtagcgggg gtggaggctc aggtggcggt ggcagttatc cttacgatgt gcccgactat 480

gcttcaggcg gggggagtat tacctgcccc cctccgatga gcgtggagca cgccgacatc 540

tgggtcaaga gctacagctt gtatagtagg gagcggtaca tctgtaacag cgggttcaag 600

aggaaggccg ggaccagctc actgaccgag tgcgtgttga acaaggccac caacgtggcc 660

cactggacca cccctagcct taagtgcatc agggacccag cgctcgtaca ccagagaccc 720

gcgcctccct ctacggtaac cacggcaggc gtaacccccc agcccgagag cctgtccccg 780

agcggcaagg agcctgcagc gagcagcccc tcaagcaaca acacagccgc taccaccgcg 840

gcaatcgtgc ccggcagcca gctgatgccc tcaaagagcc ccagcaccgg caccactgag 900

ataagcagcc acgagagctc acacggcact ccctcacaga ccactgccaa gaattgggag 960

ctgaccgcct ctgccagcca ccagccccca ggcgtgtatc cccagggcca cagcgacacc 1020

acggtcgcca tcagcacatc tacagtgctt ttgtgcggcc ttagcgccgt gtcactgctg 1080

gcatgctact tgaaaagtag gcaaactccc cctcttgcca gtgtggaaat ggaggccatg 1140

gaagccctgc ccgtgacctg gggcaccagt tctagggacg aggaccttga gaactgctca 1200

catcatttgt ga 1212

<210> 1093
<211> 1116
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1093
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttctagtg gtattacctg ccccctccg 420

atgagcgtgg agcacgccga catctgggtc aagagctaca gcttgtatag tagggagcgg 480

tacatctgta acagcgggtt caagaggaag gccgggacca gctcactgac cgagtgcgtg 540

ttgaacaagg ccaccaacgt ggcccactgg accaccccta gccttaagtg catcagggac 600

ccagcgctcg tacaccagag acccgcgcct ccctctacgg taaccacggc aggcgtaacc 660

ccccagcccg agagcctgtc cccgagcggc aaggagcctg cagcgagcag cccctcaagc 720

aacaacacag ccgctaccac cgcggcaatc gtgcccggca gccagctgat gccctcaaag 780

agccccagca ccggcaccac tgagataagc agccacgaga gctcacacgg cactccctca 840

cagaccactg ccaagaattg ggagctgacc gcctctgcca gccaccagcc cccaggcgtg 900

tatccccagg gccacagcga caccacggtc gccatcagca catctacagt gcttttgtgc 960

ggccttagcg ccgtgtcact gctggcatgc tacttgaaaa gtaggcaaac tccccctctt 1020

gccagtgtgg aaatggaggc catggaagcc ctgcccgtga cctggggcac cagttctagg 1080

gacgaggacc ttgagaactg ctcacatcat ttgtga 1116

<210> 1094
<211> 1224
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1094
atggccccgc ggcgggcgcg cggctgccgg accctcggtc tcccggcgct gctactgctg 60

ctgctgctcc ggccgccggc gacgcggggc aactgggtga atgtaataag tgatttgaaa 120

aaaattgaag atcttattca atctatgcat attgatgcta ctttatatac ggaaagtgat 180

gttcacccca gttgcaaagt aacagcaatg aagtgctttc tcttggagtt acaagttatt 240

tcacttgagt ccggagatgc aagtattcat gatacagtag aaaatctgat catcctagca 300

aacaacagtt tgtcttctaa tgggaatgta acagaatctg gatgcaaaga atgtgaggaa 360

ctggaggaaa aaaatattaa agaatttttg cagagttttg tacatattgt ccaaatgttc 420

atcaacactt cttccggtgg aggtagcggt ggagggggtt ctggtggagg aggttctgga 480

ggtggaggtt ctggcggtgg gtccttgcaa atcacgtgcc ctccccccat gtccgtggaa 540

cacgcagaca tctgggtcaa gagctacagc ttgtactcca gggagcggta catttgtaac 600

tctggtttca agcgtaaagc cggcacgtcc agcctgacgg agtgcgtgtt gaacaaggcc 660

acgaatgtcg cccactggac aacccccagt ctcaaatgca ttagagaccc tgccctggtt 720

caccaaaggc cagcgccacc ctccacagta acgacggcag gggtgacccc acagccagag 780

agcctctccc cttctggaaa agagcccgca gcttcatctc ccagctcaaa caacacagcg 840

gccacaacag cagctattgt cccgggctcc cagctgatgc cttcaaaatc accttccaca 900

ggaaccacag agataagcag tcatgagtcc tcccacggca ccccctctca gacaacagcc 960

aagaactggg aactcacagc atccgcctcc caccagccgc caggtgtgta tccacagggc 1020

cacagcgaca ccactgtggc tatctccacg tccactgtcc tgctgtgtgg gctgagcgct 1080

gtgtctctcc tggcatgcta cctcaagtca aggcaaactc ccccgctggc cagcgttgaa 1140

atggaagcca tggaggctct gccggtgact tgggggacca gcagcagaga tgaagacttg 1200

gaaaactgct ctcaccacct atga 1224

<210> 1095
<211> 1194
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1095
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaacgtga tctccgacct gaaaaagatc gaggatttga tccagagcat gcacattgac 120

gccaccctgt ataccgagtc cgacgtgcac ccgagttgca aggtgactgc catgaagtgc 180

ttcctgctgg agctgcaagt gatcagcctg gagagcggcg acgccagcat ccacgacacc 240

gtggaaaacc ttatcattct ggccaacaat agcctgagca gcaacggcaa cgtgaccgaa 300

agcggatgta aggaatgcga ggaactggaa gagaagaata tcaaagaatt cctgcaaagc 360

ttcgtgcaca tcgtgcagat gttcatcaac acttcttcag gtggcggtag tggtgggga 420

ggatctggag gcggaggaag cgggggtgga ggttcaggag gagggagctt gcaaattacc 480

tgccccctc cgatgagcgt ggagcacgcc gacatctggg tcaagagcta cagcttgtat 540

agtagggagc ggtacatctg taacagcggg ttcaagagga aggccgggac cagctcactg 600

accgagtgcg tgttgaacaa ggccaccaac gtggcccact ggaccacccc tagccttaag 660

tgcatcaggg acccagcgct cgtacaccag agacccgcgc ctccctctac ggtaaccacg 720

gcaggcgtaa ccccccagcc cgagagcctg tccccgagcg gcaaggagcc tgcagcgagc 780

agcccctcaa gcaacaacac agccgctacc accgcggcaa tcgtgcccgg cagccagctg 840

atgccctcaa agagccccag caccggcacc actgagataa gcagccacga gagctcacac 900

ggcactccct cacagaccac tgccaagaat tgggagctga ccgcctctgc cagccaccag 960

cccccaggcg tgtatcccca gggccacagc gacaccacgg tcgccatcag cacatctaca 1020

gtgcttttgt gcggccttag cgccgtgtca ctgctggcat gctacttgaa aagtaggcaa 1080

actccccctc ttgccagtgt ggaaatggag gccatggaag ccctgcccgt gacctggggc 1140

accagttcta gggacgagga ccttgagaac tgctcacatc atttgggatc ctga 1194

<210> 1096

<400> 1096
000

<210> 1097

<400> 1097
000

<210> 1098
<211> 1668
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1098
atggactgga cctggattct gtttctggtg gccgctgcca caagagtgca cagcaattgg 60

gtcaacgtga tcagcgacct gaagaagatc gaggacctga tccagagcat gcacatcgac 120

gccacactgt acaccgagtc cgatgtgcac cctagctgca aagtgaccgc catgaagtgc 180

tttctgctgg aactgcaagt gatcagcctg gaaagcggcg acgccagcat ccacgatacc 240

gtggaaaatc tgatcatcct ggccaacaac agcctgagca gcaacggcaa tgtgaccgag 300

agcggctgca aagagtgcga ggaactggaa gagaagaaca tcaaagagtt cctccagagc 360

ttcgtccaca tcgtgcagat gttcatcaac accagctctg gcggaggaag cggaggcgga 420

ggatctggtg gtggtggatc tggcggcggt ggtagtggcg gaggttctct gcaaatcacc 480

tgtcctccac ctatgagcgt ggaacacgcc gacatctggg tcaagagcta cagcctgtac 540

agcagagagc ggtacatctg caacagcggc ttcaagagaa aggccggcac aagcagcctg 600

accgagtgtg tgctgaacaa ggccacaaac gtggcccact ggaccacacc tagcctgaag 660

tgcatcagag atcccgctct ggttcaccag aggcctgctc ctccatctac agtgacaaca 720

gctggcgtga cccctcagcc tgagtctctg tctccatctg gaaaagagcc tgccgccagc 780

tctcccagct ctaacaatac tgctgccacc acagccgcca tcgtgcctgg atctcagctg 840

atgcctagca agagccctag caccggcaca acagagatca gctctcacga gtctagccac 900

ggcaccccat ctcagaccac agccaagaat tgggagctga ccgcctctgc ctctcatcag 960

ccacctggtg tttaccctca aggccactct gataccaccg tggccatcag cacaagcaca 1020

gtgctgctgt gtggactgtc tgccgtgtct ctgctggcct gctacctgaa gtctagacag 1080

acacctcctc tggccagcgt ggaaatggaa gccatggaag ctctgcctgt gacatggggc 1140

accagcagca gagatgagga cctcgagaat tgcagccacc acctgagcgg catctctctg 1200

attgcggcgc tggcagttga ctacgttatt ggcatggaaa acgcgatgcc atggaacctc 1260

ccggctgacc tggcgtggtt caaacgtaac accctgaaca aacctgtgat catgggtcgt 1320

cacacctggg aatctattgg ccgtcctctc ccgggtcgta aaaacatcat tctgtcttct 1380

cagccaggca ccgacgaccg tgttacctgg gttaaaagcg ttgacgaagc gattgctgcg 1440

tgcggtgatg ttcctgaaat tatggtgatc ggcggtggcc gtgttatcga acagttcctg 1500

ccgaaagcgc agaaactgta cctgacccac atcgacgcgg aagttgaagg tgacacccac 1560

ttcccggact acgaaccgga tgattgggag agcgtattct ccgaattcca tgatgcggat 1620

gcgcaaaact ctcattctta ctgttttgaa atcctggaac gtcgttag 1668

<210> 1099

<400> 1099
000

<210> 1100

<400> 1100
000

<210> 1101
<211> 1224
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1101
atggccccgc ggcgggcgcg cggctgccgg accctcggtc tcccggcgct gctactgctg 60

ctgctgctcc ggccgccggc gacgcggggc aactgggtga atgtaataag tgatttgaaa 120

aaaattgaag atcttattca atctatgcat attgatgcta ctttatatac ggaaagtgat 180

gttcacccca gttgcaaagt aacagcaatg aagtgctttc tcttggagtt acaagttatt 240

tcacttgagt ccggagatgc aagtattcat gatacagtag aaaatctgat catcctagca 300

aacaacagtt tgtcttctaa tgggaatgta acagaatctg gatgcaaaga atgtgaggaa 360

ctggaggaaa aaaatattaa agaatttttg cagagttttg tacatattgt ccaaatgttc 420

atcaacactt cttccggggg gggtagcggg ggaggggggtt ccggcggggg agggtctgga 480

gggggaggtt ccggcggggg gtccttgcaa atcacgtgcc ctccccccat gtccgtggaa 540

cacgcagaca tctgggtcaa gagctacagc ttgtactcca gggagcggta catttgtaac 600

tctggtttca agcgtaaagc cggcacgtcc agcctgacgg agtgcgtgtt gaacaaggcc 660

acgaatgtcg cccactggac aacccccagt ctcaaatgca ttagagaccc tgccctggtt 720

caccaaaggc cagcgccacc ctccacagta acgacggcag gggtgacccc acagccagag 780

agcctctccc cttctggaaa agagcccgca gcttcatctc ccagctcaaa caacacagcg 840

gccacaacag cagctattgt cccgggctcc cagctgatgc cttcaaaatc accttccaca 900

ggaaccacag agataagcag tcatgagtcc tcccacggca ccccctctca gacaacagcc 960

aagaactggg aactcacagc atccgcctcc caccagccgc caggtgtgta tccacagggc 1020

cacagcgaca ccactgtggc tatctccacg tccactgtcc tgctgtgtgg gctgagcgct 1080

gtgtctctcc tggcatgcta cctcaagtca aggcaaactc ccccgctggc cagcgttgaa 1140

atggaagcca tggaggctct gccggtgact tgggggacca gcagcagaga tgaagacttg 1200

gaaaactgct ctcaccacct atga 1224

<210> 1102
<211> 1722
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1102
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccccc 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggaatctc tctgattgcg 1260

gcgctggcag ttgactacgt tattggcatg gaaaacgcga tgccatggaa cctcccggct 1320

gacctggcgt ggttcaaacg taacaccctg aacaaacctg tgatcatggg tcgtcacacc 1380

tgggaatcta ttggccgtcc tctcccgggt cgtaaaaaca tcattctgtc ttctcagcca 1440

ggcaccgacg accgtgttac ctgggttaaa agcgttgacg aagcgattgc tgcgtgcggt 1500

gatgttcctg aaattatggt gatcggcggt ggccgtgtta tcgaacagtt cctgccgaaa 1560

gcgcagaaac tgtacctgac ccacatcgac gcggaagttg aaggtgacac ccacttcccg 1620

gactacgaac cggatgattg ggagagcgta ttctccgaat tccatgatgc ggatgcgcaa 1680

aactctcatt cttactgttt tgaaatcctg gaacgtcgtt ga 1722

<210> 1103
<211> 1245
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1103
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgcccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat cctga 1245

<210> 1104
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1104
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

tgcatcgtcg ctgtgtccca gaacatgggc atcggcaaga acggggacct gccctggcca 1320

ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgtttataa ggaagccatg 1620

aatcacccag gccatcttaa actatttgtg acaaggatca tgcaagactt tgaaagtgac 1680

acgtttttc cagaaattga tttggagaaa tataaacttc tgccagaata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcatt aagtacaaat ttgaagtata tgaggagaat 1800

gattga 1806

<210> 1105

<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1105
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

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ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgtttataa ggaagccatg 1620

aatcacccag gccatcttaa actatttgtg acaaggatca tgcaagactt tgaaagtgac 1680

acgtttttc cagaaattga tttggagaaa tataaacttc tgccaggata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcttt aagtacaaat ttgaagtata tgagaagaat 1800

gattga 1806

<210> 1106
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1106
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

tgcatcgtcg ctgtgtccca gaacatgggc atcggcaaga acggggacct gccctggcca 1320

ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgtttataa ggaagccatg 1620

aatcacccag gcagacttaa actatttgtg acaaggatca tgcaagactt tggaagtgac 1680

acgtttttc cagaaattga tttggagaaa tataaacttc tgccagaata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcatt aagtacaaat ttgaagtata tgagaagaat 1800

gattga 1806

<210> 1107
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1107
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

tgcatcgtcg ctgtgtccca gaacatgggc gtcggcaaga acggggacct gccctggcca 1320

ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgtttataa ggaagccatg 1620

aatcacccag gccatcttaa actatttgtg acaaggatca tgcaagactt tgaaagtgac 1680

acgtttttc cagaaattga tttggagaaa tataaacttc tgccagaata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcatt aagtacaaat ttgaagtata tgagaagaat 1800

gattga 1806

<210> 1108
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1108
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

agcaacaaca cagccgctac caccgcggca atcgtgcccg gcagccagct gatgccctca 900

aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

tcacagacca ctgccaagaa ttgggagctg accgcctctg ccagccacca gcccccaggc 1020

gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccccc 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

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ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgtttataa ggaagccatg 1620

tatcacccag gccatcttaa actatttgtg acaaggatca tgcaagactt tgaaagtgac 1680

acgttttttc cagaaattga tttggagaaa tataaacttc tgccagaata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcatt aagtacaaat ttgaagtata tgagaagaat 1800

gattga 1806

<210> 1109
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1109
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcgactac 60

aaagacgatg acgacaagaa ctgggtgaac gtgatctccg acctgaaaaa gatcgaggat 120

ttgatccaga gcatgcacat tgacgccacc ctgtataccg agtccgacgt gcacccgagt 180

tgcaaggtga ctgccatgaa gtgcttcctg ctggagctgc aagtgatcag cctggagagc 240

ggcgacgcca gcatccacga caccgtggaa aaccttatca ttctggccaa caatagcctg 300

agcagcaacg gcaacgtgac cgaaagcgga tgtaaggaat gcgaggaact ggaagagaag 360

aatatcaaag aattcctgca aagcttcgtg cacatcgtgc agatgttcat caacacttct 420

tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 480

ggtggaggca gcttgcaata cccatacgat gttccagatt acgctattac ctgccccct 540

ccgatgagcg tggagcacgc cgacatctgg gtcaagagct acagcttgta tagtagggag 600

cggtacatct gtaacagcgg gttcaagagg aaggccggga ccagctcact gaccgagtgc 660

gtgttgaaca aggccaccaa cgtggcccac tggaccaccc ctagccttaa gtgcatcagg 720

gacccagcgc tcgtacacca gagacccgcg cctccctcta cggtaaccac ggcaggcgta 780

acccccagc ccgagagcct gtccccgagc ggcaaggagc ctgcagcgag cagcccctca 840

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aagagcccca gcaccggcac cactgagata agcagccacg agagctcaca cggcactccc 960

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gtgtatcccc agggccacag cgacaccacg gtcgccatca gcacatctac agtgcttttg 1080

tgcggcctta gcgccgtgtc actgctggca tgctacttga aaagtaggca aactcccct 1140

cttgccagtg tggaaatgga ggccatggaa gccctgcccg tgacctgggg caccagttct 1200

agggacgagg accttgagaa ctgctcacat catttgggat ccggtgttgg ttcgctaaac 1260

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ccgctcagga atgaattcag atatttccag agaatgacca caacctcttc agtagaaggt 1380

aaacagaatc tggtgattat gggtaagaag acctggttct ccattcctga gaagaatcga 1440

cctttaaagg gtagaattaa tttagttctc agcagagaac tcaaggaacc tccacaagga 1500

gctcattttc tttccagaag tctagatgat gccttaaaac ttactgaaca accagaatta 1560

gcaaataaag tagacatggt ctggatagtt ggtggcagtt ctgttattaa ggaagccatg 1620

aatcacccag gccatcttaa actatttgtg acaaggatca tgcaagactt tgaaagtgac 1680

acgtttttc cagaaattga tttggagaaa tataaacttc tgccagaata cccaggtgtt 1740

ctctctgatg tccaggagga gaaaggcatt aagtacaaat ttgaagtata tgagaagaat 1800

gattga 1806

<210> 1110
<211> 2046
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1110
atggattgga cctggattct gtttctggtg gccgctgcca caagagtgca cagcaactgg 60

gtgaatgtga tcagcgacct gaagaagatc gaggatctga tccagagcat gcacattgat 120

gccaccctgt acacagaatc tgatgtgcac cctagctgta aagtgaccgc catgaagtgt 180

tttctgctgg agctgcaggt gatttctctg gaaagcggag atgcctctat ccacgacaca 240

gtggagaatc tgatcatcct ggccaacaat agcctgagca gcaatggcaa tgtgacagag 300

tctggctgta aggagtgtga ggagctggag gagaagaaca tcaaggagtt tctgcagagc 360

tttgtgcaca tcgtgcagat gttcatcaat acaagctctg gcggaggatc tggaggaggc 420

ggatctggag gaggaggcag tggaggcgga ggatctggcg gaggatctct gcagattaca 480

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tgcattagag atcctgccct ggtccaccag aggcctgccc ctccatctac agtgacaaca 720

gccggagtga cacctcagcc tgaatctctg agcccttctg gaaaagaacc tgccgccagc 780

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acaagcagca gagatgagga cctggagaat tgttctcacc acctgtcgcg aatggactac 1200

aaggacgatg acgacaagga ttataaagat gatgatgata aagattataa agacgacgat 1260

gataagtcgc gaggatccgg agctactaac ttcagcctgc tgaagcaggc tggagacgtg 1320

gaggagaacc ctggaccttt gagcaagggc gaggaggaca acatggccat catcaaggag 1380

ttcatgcgct tcaaggtgca catggagggc tccgtgaacg gccacgagtt cgagatcgag 1440

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ggcggccccc tgcccttcgc ctgggacatc ctgtccctc agttcatgta cggctccaag 1560

gcctacgtga agcaccccgc cgacatcccc gactacttga agctgtcctt ccccgagggc 1620

ttcaagtggg agcgcgtgat gaacttcgag gacggcggcg tggtgaccgt gacccaggac 1680

tcctccctgc aggacggcga gttcatctac aaggtgaagc tgcgcggcac caacttcccc 1740

tccgacggcc ccgtaatgca gaagaagacc atgggctggg aggcctcctc cgagcggatg 1800

taccccgagg acggcgccct gaagggcgag atcaagcaga ggctgaagct gaaggacggc 1860

ggccactacg acgccgaggt caagaccacc tacaaggcca agaagcccgt gcagctgccc 1920

ggcgcctaca acgtcaacat caagctggac atcacctccc acaacgagga ctacaccatc 1980

gtggaacagt acgagcgcgc cgagggccgc cactccaccg gcggcatgga cgagctgtac 2040

aagtaa 2046

<210> 1111
<211> 1959
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1111
atggattgga cctggattct gtttctggtg gccgctgcca caagagtgca cagcaactgg 60

gtgaatgtga tcagcgacct gaagaagatc gaggatctga tccagagcat gcacattgat 120

gccaccctgt acacagaatc tgatgtgcac cctagctgta aagtgaccgc catgaagtgt 180

tttctgctgg agctgcaggt gatttctctg gaaagcggag atgcctctat ccacgacaca 240

gtggagaatc tgatcatcct ggccaacaat agcctgagca gcaatggcaa tgtgacagag 300

tctggctgta aggagtgtga ggagctggag gagaagaaca tcaaggagtt tctgcagagc 360

tttgtgcaca tcgtgcagat gttcatcaat acaagctctg gcggaggatc tggaggaggc 420

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tgccctcctc caatgtctgt ggagcacgcc gatatttggg tgaagtccta cagcctgtac 540

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acagagtgcg tgctgaataa ggccacaaat gtggcccact ggacaacacc tagcctgaag 660

tgcattagag atcctgccct ggtccaccag aggcctgccc ctccatctac agtgacaaca 720

gccggagtga cacctcagcc tgaatctctg agcccttctg gaaaagaacc tgccgccagc 780

tctcctagct ctaataatac cgccgccaca acagccgcca ttgtgcctgg atctcagctg 840

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aacttcagcc tgctgaagca ggctggagac gtggaggaga accctggacc tttgagcaag 1260

ggcgaggagg acaacatggc catcatcaag gagttcatgc gcttcaaggt gcacatggag 1320

ggctccgtga acggccacga gttcgagatc gagggcgagg gcgagggccg cccctacgag 1380

ggcacccaga ccgccaagct gaaggtgacc aagggcggcc ccctgccctt cgcctgggac 1440

atcctgtccc ctcagttcat gtacggctcc aaggcctacg tgaagcaccc cgccgacatc 1500

cccgactact tgaagctgtc cttccccgag ggcttcaagt gggagcgcgt gatgaacttc 1560

gaggacggcg gcgtggtgac cgtgacccag gactcctccc tgcaggacgg cgagttcatc 1620

tacaaggtga agctgcgcgg caccaacttc ccctccgacg gccccgtaat gcagaagaag 1680

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gagatcaagc agaggctgaa gctgaaggac ggcggccact acgacgccga ggtcaagacc 1800

acctacaagg ccaagaagcc cgtgcagctg cccggcgcct acaacgtcaa catcaagctg 1860

gacatcacct cccacaacga ggactacacc atcgtggaac agtacgagcg cgccgagggc 1920

cgccactcca ccggcggcat ggacgagctg tacaagtaa 1959

<210> 1112

<400> 1112
000

<210> 1113

<400> 1113
000

<210> 1114
<211> 320
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1114
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

```
Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Gly Ser Val Gly Ser Leu Asn Cys Ile Val Ala Val
    130                 135                 140

Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro
145                 150                 155                 160

Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser
                165                 170                 175

Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe
            180                 185                 190

Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val
        195                 200                 205

Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser
    210                 215                 220

Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala
225                 230                 235                 240

Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys
                245                 250                 255

Glu Ala Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile
            260                 265                 270

Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu
        275                 280                 285

Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln
    290                 295                 300

Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
305                 310                 315                 320
```

<210> 1115
<211> 320
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1115

```
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1               5                  10                  15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
            20                  25                  30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
        35                  40                  45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
    50                  55                  60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65                  70                  75                  80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
                85                  90                  95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
            100                 105                 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
        115                 120                 125

Ile Asn Thr Ser Gly Ser Val Gly Ser Leu Asn Cys Ile Val Ala Val
    130                 135                 140

Ser Gln Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro
145                 150                 155                 160

Leu Arg Asn Glu Phe Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser
                165                 170                 175
```

```
Val Glu Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe
            180                 185                 190


Ser Ile Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val
        195                 200                 205


Leu Ser Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser
    210                 215                 220


Arg Ser Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala
225                 230                 235                 240


Asn Lys Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys
                245                 250                 255


Glu Ala Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile
            260                 265                 270


Met Gln Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu
        275                 280                 285


Lys Tyr Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln
    290                 295                 300


Glu Glu Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
305                 310                 315                 320


<210> 1116
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 1116
Met Ser Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met
1               5                   10                  15
```

```
Arg Phe Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu
            20                  25                  30

Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala
        35                  40                  45

Lys Leu Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile
    50                  55                  60

Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro
65                  70                  75                  80

Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys
                85                  90                  95

Trp Glu Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr
            100                 105                 110

Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu
        115                 120                 125

Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr
    130                 135                 140

Met Gly Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala
145                 150                 155                 160

Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His
                165                 170                 175

Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln
            180                 185                 190

Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His
        195                 200                 205

Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg
    210                 215                 220
```

His Ser Thr Gly Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 1117
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1117
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Gly Ser
130

<210> 1118
<211> 134

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1118
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1 5 10 15

His Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
20 25 30

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
35 40 45

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
50 55 60

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
65 70 75 80

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
85 90 95

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
100 105 110

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
115 120 125

Ile Asn Thr Ser Gly Ser
130

<210> 1119
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1119
Met Ser Lys Gly Glu Glu Asp Asn Met Ala Ile Ile Lys Glu Phe Met
1   5   10   15

Arg Phe Lys Val His Met Glu Gly Ser Val Asn Gly His Glu Phe Glu
            20   25   30

Ile Glu Gly Glu Gly Glu Gly Arg Pro Tyr Glu Gly Thr Gln Thr Ala
        35   40   45

Lys Leu Lys Val Thr Lys Gly Gly Pro Leu Pro Phe Ala Trp Asp Ile
    50   55   60

Leu Ser Pro Gln Phe Met Tyr Gly Ser Lys Ala Tyr Val Lys His Pro
65   70   75   80

Ala Asp Ile Pro Asp Tyr Leu Lys Leu Ser Phe Pro Glu Gly Phe Lys
                85   90   95

Trp Glu Arg Val Met Asn Phe Glu Asp Gly Gly Val Val Thr Val Thr
            100   105   110

Gln Asp Ser Ser Leu Gln Asp Gly Glu Phe Ile Tyr Lys Val Lys Leu
        115   120   125

Arg Gly Thr Asn Phe Pro Ser Asp Gly Pro Val Met Gln Lys Lys Thr
    130   135   140

Met Gly Trp Glu Ala Ser Ser Glu Arg Met Tyr Pro Glu Asp Gly Ala
145   150   155   160

Leu Lys Gly Glu Ile Lys Gln Arg Leu Lys Leu Lys Asp Gly Gly His
                165   170   175

Tyr Asp Ala Glu Val Lys Thr Thr Tyr Lys Ala Lys Lys Pro Val Gln
            180   185   190

Leu Pro Gly Ala Tyr Asn Val Asn Ile Lys Leu Asp Ile Thr Ser His
        195   200   205

Asn Glu Asp Tyr Thr Ile Val Glu Gln Tyr Glu Arg Ala Glu Gly Arg
210 215 220

His Ser Thr Gly Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 1120
<211> 2291
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1120
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggtt ccgttggttc gctaaactgc 420

atcgtcgctg tgtcccagaa catgggcatc ggcaagaacg gggacctgcc ctggccaccg 480

ctcaggaatg aattcagata tttccagaga atgaccacaa cctcttcagt agaaggtaaa 540

cagaatctgg tgattatggg taagaagacc tggttctcca ttcctgagaa gaatcgacct 600

ttaaagggta gaattaattt agttctcagc agagaactca aggaacctcc acaaggagct 660

cattttcttt ccagaagtct agatgatgcc ttaaaactta ctgaacaacc agaattagca 720

aataaagtag acatggtctg gatagttggt ggcagttctg ttattaagga agccatgaat 780

cacccaggcc atcttaaact atttgtgaca aggatcatgc aagactttga aagtgacacg 840

ttttttccag aaattgattt ggagaaatat aaacttctgc cagaataccc aggtgttctc 900

tctgatgtcc aggaggagaa aggcattaag tacaaatttg aagtatatga gaagaatgat 960

tgatctagat aatacgactc actagagatc ccgcccctct ccctcccccc cccctaacgt 1020

tactggccga agccgcttgg aataaggccg gtgtgcgttt gtctatatgt tattttccac 1080

catattgccg tcttttggca atgtgagggc ccggaaacct ggccctgtct tcttgacgag 1140

cattcctagg ggtctttccc ctctcgccaa aggaatgcaa ggtctgttga atgtcgtgaa 1200

ggaagcagtt cctctggaag cttcttgaag acaaacaacg tctgtagcga ccctttgcag 1260

gcagcggaac cccccacctg gcgacaggtg cctctgcggc caaaagccac gtgtataaga 1320

tacacctgca aaggcggcac aaccccagtg ccacgttgtg agttggatag ttgtggaaag 1380

agtcaaatgg ctctcctcaa gcgtattcaa caaggggctg aaggatgccc agaaggtacc 1440

ccattgtatg ggatctgatc tggggcctcg gtgcacatgc tttacatgtg tttagtcgag 1500

gttaaaaaaa cgtctaggcc ccccgaacca cggggacgtg gttttccttt gaaaaacacg 1560

atgataatat ggccacaacc atgatgagca agggcgagga ggataacatg gccatcatca 1620

aggagttcat gcgcttcaag gtgcacatgg agggctccgt gaacggccac gagttcgaga 1680

tcgagggcga gggcgagggc cgcccctacg agggcaccca gaccgccaag ctgaaggtga 1740

ccaagggtgg cccctgccc ttcgcctggg acatcctgtc ccctcagttc atgtacggct 1800

ccaaggccta cgtgaagcac cccgccgaca tccccgacta cttgaagctg tccttccccg 1860

agggcttcaa gtgggagcgc gtgatgaact tcgaggacgg cggcgtggtg accgtgaccc 1920

aggactcctc cctgcaggac ggcgagttca tctacaaggt gaagctgcgc ggcaccaact 1980

tcccctccga cggccccgta atgcagaaga agaccatggg ctgggaggcc tcctccgagc 2040

ggatgtaccc cgaggacggc gccctgaagg gcgagatcaa gcagaggctg aagctgaagg 2100

acggcggcca ctacgacgct gaggtcaaga ccacctacaa ggccaagaag cccgtgcagc 2160

tgcccggcgc ctacaacgtc aacatcaagt tggacatcac ctcccacaac gaggactaca 2220

ccatcgtgga acagtacgaa cgcgccgagg gccgccactc caccggcggc atggacgagc 2280

tgtacaagta a 2291

<210> 1121
<211> 963
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1121
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggtt ccgttggttc gctaaactgc 420

atcgtcgctg tgtcccagaa catgggcatc ggcaagaacg gggacctgcc ctggccaccg 480

ctcaggaatg aattcagata tttccagaga atgaccacaa cctcttcagt agaaggtaaa 540

cagaatctgg tgattatggg taagaagacc tggttctcca ttcctgagaa gaatcgacct 600

ttaaagggta gaattaattt agttctcagc agagaactca aggaacctcc acaaggagct 660

cattttcttt ccagaagtct agatgatgcc ttaaaactta ctgaacaacc agaattagca 720

aataaagtag acatggtctg gatagttggt ggcagttctg ttattaagga agccatgaat 780

cacccaggcc atcttaaact atttgtgaca aggatcatgc aagactttga aagtgacacg 840

ttttttccag aaattgattt ggagaaatat aaacttctgc cagaataccc aggtgttctc 900

tctgatgtcc aggaggagaa aggcattaag tacaaatttg aagtatatga gaagaatgat 960

tga 963

<210> 1122
<211> 708
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1122
atgagcaagg gcgaggagga taacatggcc atcatcaagg agttcatgcg cttcaaggtg 60

cacatggagg gctccgtgaa cggccacgag ttcgagatcg agggcgaggg cgagggccgc 120

ccctacgagg gcacccagac cgccaagctg aaggtgacca agggtggccc cctgcccttc 180

gcctgggaca tcctgtcccc tcagttcatg tacggctcca aggcctacgt gaagcacccc 240

gccgacatcc ccgactactt gaagctgtcc ttccccgagg gcttcaagtg ggagcgcgtg 300

atgaacttcg aggacggcgg cgtggtgacc gtgacccagg actcctccct gcaggacggc 360

gagttcatct acaaggtgaa gctgcgcggc accaacttcc cctccgacgg ccccgtaatg 420

cagaagaaga ccatgggctg ggaggcctcc tccgagcgga tgtaccccga ggacggcgcc 480

ctgaagggcg agatcaagca gaggctgaag ctgaaggacg gcggccacta cgacgctgag 540

gtcaagacca cctacaaggc caagaagccc gtgcagctgc ccggcgccta caacgtcaac 600

atcaagttgg acatcacctc ccacaacgag gactacacca tcgtggaaca gtacgaacgc 660

gccgagggcc gccactccac cggcggcatg gacgagctgt acaagtaa 708

<210> 1123
<211> 1735
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1123
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggat cctgaaatct agataatacg 420

actcactaga gatcccgccc ctctccctcc ccccccccta acgttactgg ccgaagccgc 480

ttggaataag gccggtgtgc gtttgtctat atgttatttt ccaccatatt gccgtctttt 540

ggcaatgtga gggcccggaa acctggccct gtcttcttga cgagcattcc taggggtctt 600

tcccctctcg ccaaaggaat gcaaggtctg ttgaatgtcg tgaaggaagc agttcctctg 660

gaagcttctt gaagacaaac aacgtctgta gcgacccttt gcaggcagcg gaaccccca 720

cctggcgaca ggtgcctctg cggccaaaag ccacgtgtat aagatacacc tgcaaaggcg 780

gcacaacccc agtgccacgt tgtgagttgg atagttgtgg aaagagtcaa atggctctcc 840

tcaagcgtat tcaacaaggg gctgaaggat gcccagaagg taccccattg tatgggatct 900

gatctggggc ctcggtgcac atgctttaca tgtgtttagt cgaggttaaa aaaacgtcta 960

ggcccccga accacgggga cgtggttttc ctttgaaaaa cacgatgata atatggccac 1020

aaccatgatg agcaagggcg aggaggataa catggccatc atcaaggagt tcatgcgctt 1080

caaggtgcac atggagggct ccgtgaacgg ccacgagttc gagatcgagg gcgagggcga 1140

gggccgcccc tacgagggca cccagaccgc caagctgaag gtgaccaagg gtggcccccc 1200

gcccttcgcc tgggacatcc tgtcccctca gttcatgtac ggctccaagg cctacgtgaa 1260

gcaccccgcc gacatccccg actacttgaa gctgtccttc cccgagggct tcaagtggga 1320

gcgcgtgatg aacttcgagg acggcggcgt ggtgaccgtg acccaggact cctccctgca 1380

ggacggcgag ttcatctaca aggtgaagct gcgcggcacc aacttccct ccgacggccc 1440

cgtaatgcag aagaagacca tgggctggga ggcctcctcc gagcggatgt accccgagga 1500

cggcgccctg aagggcgaga tcaagcagag gctgaagctg aaggacggcg gccactacga 1560

cgctgaggtc aagaccacct acaaggccaa gaagcccgtg cagctgcccg gcgcctacaa 1620

cgtcaacatc aagttggaca tcacctccca caacgaggac tacaccatcg tggaacagta 1680

cgaacgcgcc gagggccgcc actccaccgg cggcatggac gagctgtaca agtaa 1735

<210> 1124
<211> 405
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1124
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagcaactgg 60

gtgaatgtaa taagtgattt gaaaaaaatt gaagatctta ttcaatctat gcatattgat 120

gctactttat atacggaaag tgatgttcac cccagttgca aagtaacagc aatgaagtgc 180

tttctcttgg agttacaagt tatttcactt gagtccggag atgcaagtat tcatgataca 240

gtagaaaatc tgatcatcct agcaaacaac agtttgtctt ctaatgggaa tgtaacagaa 300

tctggatgca aagaatgtga ggaactggag gaaaaaaata ttaaagaatt tttgcagagt 360

tttgtacata ttgtccaaat gttcatcaac acttctggat cctga 405

<210> 1125
<211> 708
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1125
atgagcaagg gcgaggagga taacatggcc atcatcaagg agttcatgcg cttcaaggtg 60

cacatggagg gctccgtgaa cggccacgag ttcgagatcg agggcgaggg cgagggccgc 120

ccctacgagg gcacccagac cgccaagctg aaggtgacca agggtggccc cctgcccttc 180

gcctgggaca tcctgtcccc tcagttcatg tacggctcca aggcctacgt gaagcacccc 240

gccgacatcc ccgactactt gaagctgtcc ttccccgagg gcttcaagtg ggagcgcgtg 300

atgaacttcg aggacggcgg cgtggtgacc gtgacccagg actcctccct gcaggacggc 360

gagttcatct acaaggtgaa gctgcgcggc accaacttcc cctccgacgg ccccgtaatg 420

cagaagaaga ccatgggctg ggaggcctcc tccgagcgga tgtaccccga ggacggcgcc 480

ctgaagggcg agatcaagca gaggctgaag ctgaaggacg gcggccacta cgacgctgag 540

gtcaagacca cctacaaggc caagaagccc gtgcagctgc ccggcgccta caacgtcaac 600

atcaagttgg acatcacctc ccacaacgag gactacacca tcgtggaaca gtacgaacgc 660

gccgagggcc gccactccac cggcggcatg gacgagctgt acaagtaa 708

<210> 1126
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1126
Tyr Asp Ser Leu Glu Ile Pro Pro Leu Ser Leu Pro Pro Pro
1 5 10

<210> 1127
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1127
Arg Tyr Trp Pro Lys Pro Leu Gly Ile Arg Pro Val Cys Val Cys Leu
1 5 10 15

Tyr Val Ile Phe His His Ile Ala Val Phe Trp Gln Cys Glu Gly Pro
20 25 30

Glu Thr Trp Pro Cys Leu Leu Asp Glu His Ser
35 40

<210> 1128
<211> 102
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1128
Gly Ser Phe Pro Ser Arg Gln Arg Asn Ala Arg Ser Val Glu Cys Arg
1 5 10 15

Glu Gly Ser Ser Ser Ser Gly Ser Phe Leu Lys Thr Asn Asn Val Cys
20 25 30

Ser Asp Pro Leu Gln Ala Ala Glu Pro Pro Thr Trp Arg Gln Val Pro
35 40 45

Leu Arg Pro Lys Ala Thr Cys Ile Arg Tyr Thr Cys Lys Gly Gly Thr
50 55 60

Thr Pro Val Pro Arg Cys Glu Leu Asp Ser Cys Gly Lys Ser Gln Met
65 70 75 80

Ala Leu Leu Lys Arg Ile Gln Gln Gly Ala Glu Gly Cys Pro Glu Gly
85 90 95

Thr Pro Leu Tyr Gly Ile
100

<210> 1129
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1129
Ser Gly Ala Ser Val His Met Leu Tyr Met Cys Leu Val Glu Val Lys
1 5 10 15

Lys Thr Ser Arg Pro Pro Glu Pro Arg Gly Arg Gly Phe Pro Leu Lys
20 25 30

Asn Thr Met Ile Ile Trp Pro Gln Pro
35 40

<210> 1130
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1130
Ala Arg Ala Arg Arg Ile Thr Trp Pro Ser Ser Arg Ser Ser Cys Ala
1 5 10 15

Ser Arg Cys Thr Trp Arg Ala Pro
20

<210> 1131
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1131
Thr Ala Thr Ser Ser Arg Ser Arg Ala Arg Ala Arg Ala Ala Pro Thr
1 5 10 15

Arg Ala Pro Arg Pro Pro Ser
20

<210> 1132
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1132
Pro Arg Val Ala Pro Cys Pro Ser Pro Gly Thr Ser Cys Pro Leu Ser
1 5 10 15

Ser Cys Thr Ala Pro Arg Pro Thr
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<210> 1133
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1133

Ser Thr Pro Pro Thr Ser Pro Thr Thr
1 5

<210> 1134
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1134
Ser Cys Pro Ser Pro Arg Ala Ser Ser Gly Ser Ala
1 5 10

<210> 1135
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1135
Thr Ser Arg Thr Ala Ala Trp
1 5

<210> 1136
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1136
Pro Arg Thr Pro Pro Cys Arg Thr Ala Ser Ser Ser Thr Arg
1 5 10

<210> 1137
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
construct

<400> 1137
Ser Cys Ala Ala Pro Thr Ser Pro Pro Thr Ala Pro
1 5 10

<210> 1138
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1138
Cys Arg Arg Arg Pro Trp Ala Gly Arg Pro Pro Pro Ser Gly Cys Thr
1 5 10 15

Pro Arg Thr Ala Pro
20

<210> 1139
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1139
Arg Ala Arg Ser Ser Arg Gly
1 5

<210> 1140
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1140
Arg Thr Ala Ala Thr Thr Thr Leu Arg Ser Arg Pro Pro Thr Arg Pro
1 5 10 15

Arg Ser Pro Cys Ser Cys Pro Ala Pro Thr Thr Ser Thr Ser Ser Trp
            20   25   30

Thr Ser Pro Pro Thr Thr Arg Thr Thr Pro Ser Trp Asn Ser Thr Asn
        35   40   45

Ala Pro Arg Ala Ala Thr Pro Pro Ala Ala Trp Thr Ser Cys Thr Ser
    50   55   60

<210> 1141
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 1141
Asn Leu Asp Asn Thr Thr His
1   5

<210> 1142
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      construct

<400> 1142
Arg Ser Arg Pro Ser Pro Ser Pro Pro Pro Asn Val Thr Gly Arg Ser
1   5   10   15

Arg Leu Glu

<210> 1143
<211> 60
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
construct

<400> 1143
Gly Arg Cys Ala Phe Val Tyr Met Leu Phe Ser Thr Ile Leu Pro Ser
1 5 10 15

Phe Gly Asn Val Arg Ala Arg Lys Pro Gly Pro Val Phe Leu Thr Ser
20 25 30

Ile Pro Arg Gly Leu Ser Pro Leu Ala Lys Gly Met Gln Gly Leu Leu
35 40 45

Asn Val Val Lys Glu Ala Val Pro Leu Glu Ala Ser
50 55 60

<210> 1144
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1144
Arg Gln Thr Thr Ser Val Ala Thr Leu Cys Arg Gln Arg Asn Pro Pro
1 5 10 15

Pro Gly Asp Arg Cys Leu Cys Gly Gln Lys Pro Arg Val
20 25

<210> 1145
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1145
Asp Thr Pro Ala Lys Ala Ala Gln Pro Gln Cys His Val Val Ser Trp
1 5 10 15

Ile Val Val Glu Arg Val Lys Trp Leu Ser Ser Ser Val Phe Asn Lys
20 25 30

Gly Leu Lys Asp Ala Gln Lys Val Pro His Cys Met Gly Ser Asp Leu
35 40 45

Gly Pro Arg Cys Thr Cys Phe Thr Cys Val
50 55

<210> 1146
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1146
Ser Arg Leu Lys Lys Arg Leu Gly Pro Pro Asn His Gly Asp Val Val
1 5 10 15

Phe Leu

<210> 1147
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1147
Tyr Gly His Asn His Asp Glu Gln Gly Arg Gly Gly
1 5 10

<210> 1148
<211> 171
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1148
His Gly His His Gln Gly Val His Ala Leu Gln Gly Ala His Gly Gly
1   5   10   15

Leu Arg Glu Arg Pro Arg Val Arg Asp Arg Gly Arg Gly Arg Gly Pro
            20   25   30

Pro Leu Arg Gly His Pro Asp Arg Gln Ala Glu Gly Asp Gln Gly Trp
        35   40   45

Pro Pro Ala Leu Arg Leu Gly His Pro Val Pro Ser Val His Val Arg
    50   55   60

Leu Gln Gly Leu Arg Glu Ala Pro Arg Arg His Pro Arg Leu Leu Glu
65   70   75   80

Ala Val Leu Pro Arg Gly Leu Gln Val Gly Ala Arg Asp Glu Leu Arg
                85   90   95

Gly Arg Arg Arg Gly Asp Arg Asp Pro Gly Leu Leu Pro Ala Gly Arg
            100   105   110

Arg Val His Leu Gln Gly Glu Ala Ala Arg His Gln Leu Pro Leu Arg
        115   120   125

Arg Pro Arg Asn Ala Glu Glu Asp His Gly Leu Gly Gly Leu Leu Arg
    130   135   140

Ala Asp Val Pro Arg Gly Arg Arg Pro Glu Gly Arg Asp Gln Ala Glu
145   150   155   160

Ala Glu Ala Glu Gly Arg Arg Pro Leu Arg Arg
                165   170

<210> 1149
<211> 56
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic construct

<400> 1149
Gly Gln Asp His Leu Gln Gly Gln Glu Ala Arg Ala Ala Ala Arg Arg
1 5 10 15

Leu Gln Arg Gln His Gln Val Gly His His Leu Pro Gln Arg Gly Leu
20 25 30

His His Arg Gly Thr Val Arg Thr Arg Arg Gly Pro Pro Leu His Arg
35 40 45

Arg His Gly Arg Ala Val Gln Val
50 55

<210> 1150

<400> 1150
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<210> 1151

<400> 1151
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<210> 1152

<400> 1152
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<210> 1213

<400> 1213
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<210> 1214

<400> 1214
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<210> 1215
<211> 604
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

construct

<400> 1215

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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 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
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        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
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405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg Thr Arg Tyr Pro Tyr Asp Val Pro Asp Tyr
485 490 495

Ala Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe
500 505 510

Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly
515 520 525

Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys
530 535 540

Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val
545 550 555 560

Ala Gln Met Ser Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp
565 570 575

Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala
580 585 590

Thr Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
595 600

<210> 1216

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1216
Met His Arg Ser Ala Ala Ala Ala Thr
1 5

<210> 1217
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1217
Ile Pro Pro Pro Pro Pro Leu Ser Leu Pro Pro Pro
1 5 10

<210> 1218
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1218
Arg Tyr Trp Pro Lys Pro Leu Gly Ile Arg Pro Val Cys Val Cys Leu
1 5 10 15

Tyr Val Ile Phe His His Ile Ala Val Phe Trp Gln Cys Glu Gly Pro
20 25 30

Glu Thr Trp Pro Cys Leu Leu Asp Glu His Ser
35 40

<210> 1219
<211> 102
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1219
Gly Ser Phe Pro Ser Arg Gln Arg Asn Ala Arg Ser Val Glu Cys Arg
1 5 10 15

Glu Gly Ser Ser Ser Ser Gly Ser Phe Leu Lys Thr Asn Asn Val Cys
20 25 30

Ser Asp Pro Leu Gln Ala Ala Glu Pro Pro Thr Trp Arg Gln Val Pro
35 40 45

Leu Arg Pro Lys Ala Thr Cys Ile Arg Tyr Thr Cys Lys Gly Gly Thr
50 55 60

Thr Pro Val Pro Arg Cys Glu Leu Asp Ser Cys Gly Lys Ser Gln Met
65 70 75 80

Ala Leu Leu Lys Arg Ile Gln Gln Gly Ala Glu Gly Cys Pro Glu Gly
85 90 95

Thr Pro Leu Tyr Gly Ile
100

<210> 1220
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1220
Ser Gly Ala Ser Val His Met Leu Tyr Met Cys Leu Val Glu Val Lys
1 5 10 15

Lys Thr Ser Arg Pro Pro Glu Pro Arg Gly Arg Gly Phe Pro Leu Lys
20 25 30

Asn Thr Met Ile Ile Trp Pro Gln Pro
35 40

<210> 1221
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1221
Ala Arg Ala Arg Arg Ile Thr Trp Pro Ser Ser Arg Ser Ser Cys Ala
1 5 10 15

Ser Arg Cys Thr Trp Arg Ala Pro
20

<210> 1222
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1222
Thr Ala Thr Ser Ser Arg Ser Arg Ala Arg Ala Arg Ala Ala Pro Thr
1 5 10 15

Arg Ala Pro Arg Pro Pro Ser
20

<210> 1223
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1223
Pro Arg Val Ala Pro Cys Pro Ser Pro Gly Thr Ser Cys Pro Leu Ser

1 5 10 15

Ser Cys Thr Ala Pro Arg Pro Thr
20

<210> 1224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1224
Ser Thr Pro Pro Thr Ser Pro Thr Thr
1 5

<210> 1225
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1225
Ser Cys Pro Ser Pro Arg Ala Ser Ser Gly Ser Ala
1 5 10

<210> 1226
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1226
Thr Ser Arg Thr Ala Ala Trp
1 5

<210> 1227
<211> 14
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1227
Pro Arg Thr Pro Pro Cys Arg Thr Ala Ser Ser Ser Thr Arg
1 5 10

<210> 1228
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1228
Ser Cys Ala Ala Pro Thr Ser Pro Pro Thr Ala Pro
1 5 10

<210> 1229
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1229
Cys Arg Arg Arg Pro Trp Ala Gly Arg Pro Pro Pro Ser Gly Cys Thr
1 5 10 15

Pro Arg Thr Ala Pro
20

<210> 1230
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
construct

<400> 1230
Arg Ala Arg Ser Ser Arg Gly
1 5

<210> 1231
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic construct

<400> 1231
Arg Thr Ala Ala Thr Thr Thr Leu Arg Ser Arg Pro Pro Thr Arg Pro
1 5 10 15

Arg Ser Pro Cys Ser Cys Pro Ala Pro Thr Thr Ser Thr Ser Ser Trp
20 25 30

Thr Ser Pro Pro Thr Thr Arg Thr Thr Pro Ser Trp Asn Ser Thr Asn
35 40 45

Ala Pro Arg Ala Ala Thr Pro Pro Ala Ala Trp Thr Ser Cys Thr Ser
50 55 60

<210> 1232
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic FLAG sequence

<400> 1232
Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 1233
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

linker sequence

<400> 1233
Gly Gly Gly Gly
1

<210> 1234
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
linker sequence

<400> 1234
Gly Gly Gly Gly Gly Gly Gly Gly
1 5

<210> 1235
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<220>
<221> MOD_RES
<222> (2)..(2)
<223> Val or Ile

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Any amino acid

<400> 1235
Asp Xaa Glu Xaa Asn Pro Gly Pro
1 5