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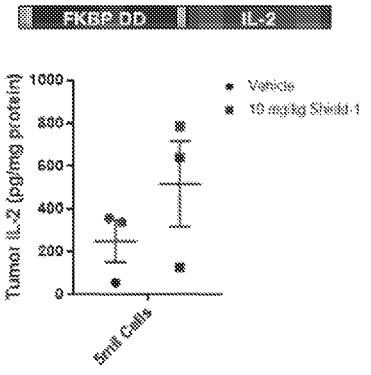
(54) Title: COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

(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.

Figure 19



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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, US Provisional Patent Application No. 62/484,063, filed on April 11, 2017 entitled Compositions and Methods for Immunotherapy, and US Provisional Patent Application 62/542,402, filed on August 8, 2017 entitled 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_1207PCT_SL.txt, created on March 2, 2018, which is 1,566,189 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 each of which are herein incorporated by reference in their entirety).

[0010] In some embodiments, the composition for inducing an immune response may comprise a first effector module. In some embodiments, the effector module may comprise a first

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 cytokine, a safety switch, a regulatory switch, a chimeric antigen receptor and combinations thereof.

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

[0013] In some embodiments, the first 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 having at least one mutation selected from 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, 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.

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

[0016] In some embodiments, the immunotherapeutic agent may be a cytokine. In one aspect, the cytokine may be an interleukin, an interferon, a tumor necrosis factor, a transforming growth factor B, a CC chemokine, a CXC chemokine, a CX3C chemokine or a growth factor. In some embodiments, the cytokine is an interleukin. In some embodiments, the interleukin is selected from a group consisting of IL1, IL1-alpha, IL1-beta, IL1-delta, IL1-epsilon, IL1-eta, IL1-zeta, IL-RA, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL10C, IL10D, IL11a, IL11b, IL13, IL14, IL16, IL17, IL-17A, IL17B, IL17C, IL17E, IL17F, IL18, IL19, IL20, IL20L, IL21, IL22, IL23, IL23A, IL24, IL25, IL26, IL27, IL28, IL29, IL30, IL31, IL32, IL33, IL34, IL36α, IL36β, IL36γ, IL36RN, IL37, IL37a, IL37b, IL37c, Il37d, IL37e, and IL38.

[0017] In one aspect, the interleukin may be IL2, comprising the amino acid sequence of SEQ ID NO. 51.

[0018] In one aspect, the immunotherapeutic agent may be a safety switch. In some embodiments, the safety switch may be selected from a Caspase 9, an inducible FAS (iFAS), an inducible caspase 9 (icasp9), a CD20/anti-CD20 antibody pair, a protein tag/anti-tag antibody, and a compact suicide gene (RQR8). In one aspect, the safety switch may be Caspase 9 comprising the amino acid sequence of SEQ ID NO. 65.

[0019] In one aspect, the immunotherapeutic agent may encode a regulatory switch. In some embodiments, the regulatory switch may be selected from a FOXP3, a Nr4a, a FOXO, and a NF-κB. In one aspect, the regulatory switch may be a FOXP3, comprising the amino acid sequence of SEQ ID NO. 103-106.

[0020] In one aspect, the immunotherapeutic agent may be a chimeric antigen receptor (CAR). In some embodiments, the CAR may be selected from a GD2 CAR, a Her2 CAR, a BCMA CAR, a CD33 CAR, an ALK CAR, a CD22 CAR, and a CD276 CAR. The CARs described herein may comprise an extracellular moiety, a transmembrane domain, an intracellular signaling domain, and optionally, one or more co-stimulatory domains.

[0021] 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.

[0022] 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.

[0023] In some embodiments, the extracellular target moiety may be selected from an ALK target moiety, comprising the amino acid sequence of SEQ ID NO. 242- 257 and 422-429, a CD22 target moiety, comprising the amino acid sequence of SEQ ID NO.258-262 and 430-432, a CD276 target moiety, comprising the amino acid sequence of SEQ ID NO. 263-270 and 433-436, a GD2 target moiety, comprising the amino acid sequence of SEQ ID NO.271-349 and 437-465, a CD33 target moiety, comprising the amino acid sequence of SEQ ID NO. 350-357, a BCMA target moiety, comprising the amino acid sequence of SEQ ID NO. 358-365, and a Her2 target moiety, comprising the amino acid sequence of SEQ ID NO. 366-421 and 466-473.

[0024] In some embodiments, the intracellular signaling domain of the CAR may be derived from T cell receptor CD3zeta or 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.

[0025] In some embodiments, the CAR may comprise a co-stimulatory domain. The costimulatory 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.

[0026] In one embodiment, the transmembrane domain of the CAR may be derived from a transmembrane domain. In one aspect, the transmembrane domain may comprise the amino acid sequence selected from, but not limited to SEQ ID NO. 527-624.

[0027] 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. 628-694.

[0028] In one aspect, the first effector module may comprise an IL2-DD, comprising the amino acid sequence of any of SEQ ID NOs. 52-54.

[0029] In one aspect, the first effector module may comprise a Caspase 9-DD, comprising the amino acid sequence of any of SEQ ID NOs. 72-80.

[0030] In one aspect, the first effector module may comprise a FOXP3-DD, comprising the amino acid sequence of any of SEQ ID NOs. 107-116.

[0031] In one aspect, the first effector module may comprise a BCMA CAR-DD, comprising the amino acid sequence of any of SEQ ID NOs. 775-777.

[0032] In one aspect, the first effector module may comprise a HER2-DD, comprising the amino acid sequence of any of SEQ ID NO. 906.

[0033] The present invention, also provides polynucleotides encoding 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 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. In some embodiments, the polynucleotides may comprise spatiotemporally selected codons.

[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 one aspect, the immune cell may comprise a destabilizing domain DD, wherein the DD is derived from human protein FKBP comprising the amino acid sequence of SEQ ID NO. 3, DHFR comprising the amino acid sequence of SEQ ID NO. 1-2, 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 and NQO2 comprising the amino acid sequence of SEQ ID NO. 7.

[0039] In one aspect, the DD may be derived from a parent protein and the parent protein is hDHFR and the DD comprises a mutant protein having at least one mutation selected from 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, 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.

[0040] In some embodiments, the immune cells may be autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

[0041] 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.

[0042] 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.

[0043] The present invention also provides methods for preventing or reversing T cell exhaustion in a subject in need thereof. Such methods may comprise administering to the subject, a therapeutically effective amount of compositions described herein, the polynucleotides of the invention, the vectors of the invention, or the immune cells described herein. Such methods may comprise an SRE that responds to a stimulus and tunes the expression and/or function of the immunotherapeutic agent, thereby preventing or reversing T cell exhaustion.

[0044] In some aspects, the immunotherapeutic agent is a chimeric antigen receptor. In some embodiments, the chimeric antigen receptor may be a GD2 CAR, a BCMA CAR, a CD33 CAR, a Her2 CAR, an ALK CAR, a CD22 CAR, or a CD276 CAR.

[0045] Also provided herein, is a method for detecting cancer in a mammal, comprising the steps of (a) contacting a sample comprising one or more cells from the mammal with the

compositions, the polynucleotides, the vector or the immune cells of the invention, and (b) detecting the complex, wherein the detection of the complex may be indicative of the presence of cancer in the mammal.

[0046] In some embodiments, the effector module comprises a stimulus response element (SRE) and at least one payload comprising a protein of interest (POI).

[0047] 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.

[0048] The payload may be any immunotherapeutic agent used for cancer immunotherapy such as a cytokine such as IL2, a safety switch such as Caspase 9, a regulatory switch encoding FOXP3, a chimeric antigen receptor such as BCMA CAR, CD33 CAR, GD2 CAR, Her2 CAR, ALK CAR, CD22 CAR, CD276 CAR 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] In some embodiments, the vector of the invention may be a non-viral vector, such as a nanoparticles and liposomes.

[0053] 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).

[0054] 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 and methods for preventing or reversing T cell exhaustion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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).

[0065] 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.

[0066] 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).

[0067] Figure 13 is a line graph depicting the effect of Shield-1 on DD-IL2 levels.

[0068] Figure 14 denotes the frequency of IFNgamma positive T cells.

[0069] Figure 15A depicts IFN gamma production in T cells. Figure 15B depicts T cell expansion with IL15/IL15Ra treatment. Figure 15C is a dot plot depicting percentage human cells after *in vivo* cell transfer. Figure 15D is scatter plot depicting CD4+/CD8+ T cells.

[0070] Figure 16A is a western blot depicting luciferase levels in DD-luciferase expressing cells. Figure 16B depicts luciferase activity.

[0071] Figure 17A and Figure 17B are western blot depicting DD regulated expression of FOXP3.

[0072] Figure 18 is a bar graph representing the effect of promoters on transgene expression.

[0073] Figure 19 represents Shield-1 regulation of DD-IL2 secretion from HCT116 cells *in vivo*.

[0074] Figure 20 depicts the viability of T cells cultured with different ratios of CD3/CD8 beads.

[0075] Figure 21 represents the percentage BCMA CAR positive T cells with ligand treatment.

DETAILED DESCRIPTION OF THE INVENTION

[0076] 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

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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

[0084] 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 are 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 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.

[0085] 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.

[0086] 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

[0087] 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.

[0088] 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.

[0089] 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%.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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, compositions of the invention may be engineered 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 major histocompatibility complex (MHC) proteins. For example, amino acid modifications may be engineered such that the minimum number of immune epitopes are available 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 useful in 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.

[0098] Epitope identification and subsequent sequence modification may be applied to reduce immunogenicity. The identification of immunogenic epitopes may be achieved using physical or computational methods. Physical methods of epitope identification may include, for example, mass spectrometry and tissue culture/cellular techniques. Computational approaches use antigen processing, loading and display information, structural and/or proteomic data to identify non-self-peptides produced by antigen processing with good MHC groove binding characteristics. 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.

[0099] Protein modifications may also be employed to interfere with antigen processing and peptide loading e.g. glycosylation and PEGylation. Compositions of the invention may also be engineered to include non-classical amino acid side chains 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).

[00100] 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.

[00101] In some embodiments, reduced immunogenicity may be achieved by limiting immunoproteasome 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).

[00102] Another embodiment of the invention provides a method of detecting the presence of cancer in a mammal, comprising: (a) contacting a sample comprising one or more cells from the mammal with any of the CARs, nucleic acids, recombinant expression vectors, host cells, population of cells, or pharmaceutical compositions of the invention, thereby forming a complex, (b) and detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal. The sample may be obtained by any suitable method, e.g., biopsy or necropsy. A biopsy is the removal of tissue and/or cells from an individual. Such removal may be to collect tissue and/or cells from the individual in order to perform experimentation on the removed tissue and/or cells. This experimentation may also be used to determine if the individual has and/or is suffering from cancer.

[00103] With respect to an embodiment of the inventive method of detecting the presence of cancer in a mammal, the sample comprising cells of the mammal can be a sample comprising whole cells, lysates thereof, or a fraction of the whole cell lysates, e.g., a nuclear or cytoplasmic fraction, a whole protein traction, or a nucleic acid fraction. If the sample comprises whole cells, the cells can be any cells of the mammal, e.g., the cells of any organ or tissue, including tumor cells. The contacting can take place in vitro or in vivo with respect, to the mammal. Preferably, the contacting is in vitro. Also, detection of the complex can occur through any number of ways known in the art. For instance, the inventive CARs, nucleic acids, recombinant expression vectors, host cells, populations of cells, or pharmaceutical compositions described herein can be labeled with a detectable label such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles). Methods of testing the compositions of the invention for the ability to recognize target cells and for antigen specificity are known in the art. For instance, Clay et al, J. Immunol, 163: 507-51 3 (1999), teaches methods of measuring the release of cytokines (e.g., interferon-γ, granulocyte/monocyte colony stimulating factor (GM-CSF), tumor necrosis factor a (TNF-a) or interleukin 2 (IL2)). In addition, anti-CD276 material function can be evaluated by measurement of cellular cytotoxicity, as described in Zhao et al., J. Immunol, 1 74: 44) 5-4423 (2005).

[00104] 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.

[00105] 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.

1. Destabilizing domains (DDs)

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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).

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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 Application NOs. 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 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 NOS.	Ligands
E. coli Dihydrofolate reductase (ecDHFR) (Uniprot ID: P0ABQ4)	MISLIAALAVDRVIGMENAMPWNLPADLAWFKRNT LNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVT WVKSVDEAIAACGDVPEIMVIGGGRVYEQFLPKAQK LYLTHIDAEVEGDTHFPDYEPDDWESVFSEFHDADA QNSHSYCFEILERR	1	Methotrexate (MTX) Trimethoprim (TMP)
Human Dihydrofolate reductase (hDHFR) (Uniprot ID: P00374)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQ RMTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRIN LVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKV DMVWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFES DTFFPEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEV YEKND	2	Methotrexate (MTX) Trimethoprim (TMP)
FK506 binding protein (FKBP) (Uniprot ID: P62942)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKF DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQR AKLTISPDYAYGATGHPGIIPPHATLVFDVELLKLE	3	Shield-1
Phosphodiesterase 5 (PDE5), ligand binding domain (Uniprot ID: Uniprot ID O76074)	MEETRELQSLAAAVVPSAQTLKITDFSFSDFELSDLET ALCTIRMFTDLNLVQNFQMKHEVLCRWILSVKKNYR KNVAYHNWRHAFNTAQCMFAALKAGKIQNKLTDL EILALLIAALSHDLDHRGVNNSYIQRSEHPLAQLYCH SIMEHHHFDQCLMILNSPGNQILSGLSIEEYKTTLKIIK QAILATDLALYIKRRGEFFELIRKNQFNLEDPHQKELF LAMLMTACDLSAITKPWPIQQRIAELVATEFFDQGDR ERKELNIEPTDLMNREKKNKIPSMQVGFIDAICLQLY EALTHVSEDCFPLLDGCRKNRQKWQALAEQQ	4	Sildenafil; Vardenafil; Tadalafil
PPAR gamma (PPARg), ligand binding domain (Uniprot ID: P37231; amino acids 317-505)	SVEAVQEITEYAKSIPGFVNLDLNDQVTLLKYGVHEII YTMLASLMNKDGVLISEGQGFMTREFLKSLRKPFGD FMEPKFEFAVKFNALELDDSDLAIFIAVIILSGDRPGL LNVKPIEDIQDNLLQALELQLKLNHPESSQLFAKLLQ KMTDLRQIVTEHVQLLQVIKKTETDMSLHPLLQEIYK DLY	5	Posiglitazone Pioglitazone

Carbonic anhydrase II (CA2) (Uniprot ID: P00918)	MSHHWGYGKHNGPEHWHKDFPIAKGERQSPVDIDT HTAKYDPSLKPLSVSYDQATSLRILNNGHAFNVEFD DSQDKAVLKGGPLDGTYRLIQFHFHWGSLDGQGSEH TVDKKKYAAELHLVHWNTKYGDFGKAVQQPDGLA VLGIFLKVGSAKPGLQKVVDVLDSIKTKGKSADFTNF DPRGLLPESLDYWTYPGSLTTPPLLECVTWIVLKEPIS VSSEQVLKFRKLNFNGEGEPEELMVDNWRPAQPLKN RQIKASFK	6	Celecoxib Acetazolamide
NRH: Quinone oxidoreductase 2 (NQO2) (Uniprot ID: P16083)	MAGKKVLIVYAHQEPKSFNGSLKNVAVDELSRQGC TVTVSDLYAMNLEPRATDKDITGTLSNPEVFNYGVE THEAYKQRSLASDITDEQKKVREADLVIFQFPLYWFS VPAILKGWMDRVLCQGFAFDIPGFYDSGLLQGKLAL LSVTTGGTAEMYTKTGVNGDSRYFLWPLQHGTLHF CGFKVLAPQISFAPEIASEEERKGMVAAWSQRLQTIW KEEPIPCTAHWHFGQ	7	Imatinib Melatonin
Dipeptidyl peptidases (DPPIV) (Uniprot ID: P27487)	MKTPWKVLLGLLGAAALVTIITVPVVLLNKGTDDAT ADSRKTYTLTDYLKNTYRLKLYSLRWISDHEYLYKQ ENNILVFNAEYGNSSVFLENSTFDEFGHSINDYSISPD GQFILLEYNYVKQWRHSYTASYDIYDLNKRQLITEER IPNNTQWVTWSPVGHKLAYVWNNDIYVKIEPNLPSY RITWTGKEDIIYNGITDWVYEEEVFSAYSALWWSPN GTFLAYAQFNDTEVPLIEYSFYSDESLQYPKTVRVPY PKAGAVNPTVKFFVVNTDSLSSVTNATSIQITAPASM LIGDHYLCDVTWATQERISLQWLRRIQNYSVMDICD YDESSGRWNCLVARQHIEMSTTGWVGRFRPSEPHFT LDGNSFYKIISNEEGYRHICYFQIDKKDCTFITKGTWE VIGIEALTSDYLYYISNEYKGMPGGRNLYKIQLSDYT KVTCLSCELNPERCQYYSVSFSKEAKYYQLRCSGPG LPLYTLHSSVNDKGLRVLEDNSALDKMLQNVQMPS KKLDFIILNETKFWYQMILPPHFDKSKKYPLLLDVYA GPCSQKADTVFRLNWATYLASTENIIVASFDGRGSG YQGDKIMHAINRRLGTFEVEDQIEAARQFSKMGFVD NKRIAIWGWSYGGYVTSMVLGSGSGVFKCGIAVAPV SRWEYYDSVYTERYMGLPTPEDNLDHYRNSTVMSR AENFKQVEYLLIHGTADDNVHFQQSAQISKALVDVG VDFQAMWYTDEDHGIASSTAHQHIYTHMSHFIKQCF SLP	224	Sitagliptin, Saxagliptin, Denagliptin

[00115] 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)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNKP VIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVKSVDE AIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHIDAEVEG DTHFPDYEPDDWESVFSEFHDADAQNSHSYCFEILERR	8
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNKPVI MGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVKSVDEAI AACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHIDAEVEGDT HFPDYEPDDWESVFSEFHDADAQNSHSYCFEILERR	9

ecDHFR (Amino acid 2-159 of WT) (R12H, E129K)	ISLIAALAVDHVIGMENAMPWNLPADLAWFKRNTLNKPVI MGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVKSVDEAI AACGDVPEIMVIGGGRVYEQFLPKAQKLYLTHIDAEVEGD THFPDYKPDDWESVFSEFHDADAQNSHSYCFEILERR	10
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKVDSSR DRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRAKLTISPD YAYGATGHPGIIPPHATLVFDVELLKPE	11
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKVDSSR DRNKPFKFMLGKQEVIRGWEEGVAQMSVGQGAKLTISPD YAYGATGHPGIIPPHATLVFDVELLELE	12

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] In one aspect of the invention, the DHFR DDs of the invention may include mutations such as, but not limited to 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, 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.

[00125] In one embodiment, the stimulus is a small molecule that binds to a SRE in order 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, the mutations are underlined and in bold. 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	225
hDHFR (V2A, R33G, Q36R, L100P, K185R)	MAGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFGYFRR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKPTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKFEVYERND	226
hDHFR (G16S, I17V, F89L, D96G, K123E, M140V, D146G, K156R)	MVGSLNCIVAVSQNMSVGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHLLSRSLDGALKLTEQPELANKVDMVW	227

	IVGGSSVYEEAMNHPGHLKLFVTRIVQDFESGTFFPEIDL ERYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	
hDHFR (F35L, R37G, N65A, L68S, K69E, R71G, L80P, K99G, G117D, L132P, I139V, M140I, D142G, D146G, E173G, D187G)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYLQG MTTTSSVEGKQNLVIMGKKTWFSIPEKARPSEGGINLVL SREPKEPPQGAHFLSRSLDDALGLTEQPELANKVDMVW IVDGSSVYKEAMNHPGHPKLFVTRVIQGFESGTFFPEIDL EKYKLLPEYPGVLSDVQEGKGIKYKFEVYEKNG	228
hDHFR (I17N, L98S, K99R, M112T, E151G, E162G, E172G)	MVGSLNCIVAVSQNMGNGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDASRLTEQPELANKVDTVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPGIDL EKYKLLPGYPGVLSDVQGEKGIKYKFEVYEKND	229
hDHFR (R138G, D142G, F143S, K156R, K158E, E162G, V166A, K177E, Y178C, K185E, N186S)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW IVGGSSVYKEAMNHPGHLKLFVTGIMQGSESDTFFPEID LERYELLPGYPGALSDVQEEKGIECKFEVYEESD	230
hDHFR (K81R, K99R, L100P, E102G, N108D, K123R, H128R, D142G, F180L, K185E)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELREPPQGAHFLSRSLDDALRPTGQPELADKVDMVW IVGGSSVYREAMNRPGHLKLFVTRIMQGFESDTFFPEID LEKYKLLPEYPGVLSDVQEEKGIKYKLEVYEEND	231
hDHFR (N14S, P24S, F35L, M53T, K56E, R92G, S93G, N127S, H128Y, F135L, F143S, L159P, L160P, E173A, F180L)	MVGSLNCIVAVSQSMGIGKNGDLSWPPLRNEFRYLQRM TTTSSVEGKQNLVITGKETWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSGGLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMSYPGHLKLLVTRIMQDSESDTFFPEIDLE KYKPPPEYPGVLSDVQEAKGIKYKLEVYEKND	232
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	233
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	234
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)	MVGSLNCIVTVSRSMGIGKDGDLSWPPLRSEFRYFQRTT ATSSVEGRQSLVIMGKRTWFSTPERNRPLRGRANLVLS GELKGPPQGAHLLSRSLDGALKLTEQPELADKVDVVRI VGGSSVDEEAMNHPGHLKLFVTRVMRGFESDTLFPGID LGKRKLLPEYPGVLSDVREEKGIKYKLEVCGNN	235
hDHFR (Amino acid 2-187 of WT; I17V, Y122I)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	236
hDHFR (Amino acid 2-187 of WT; Y122I, M140I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIIQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	237
hDHFR (Amino acid 2-187 of WT; N127Y, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV	238

	GGSSVIKEAMYHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	
hDHFR (Amino acid 2-187 of WT; Y122I, H131R, E144G)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGRLKLFVTRIMQDFGSDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	239
hDHFR (Amino acid 2-187 of WT; D22S, F32M, R33S, Q36S, N65S)	VGSLNCIVAVSQNMGIGKNGSLPWPPLRNEMSYFSRMT TTSSVEGKQNLVIMGKKTWFSIPEKSRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	240
hDHFR (Amino acid 2-187 of WT; E31D, F32M, V116I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNDMRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWII GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	241
hDHFR (Amino acid 2-187 of WT; E162G, I176F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPGYPGVLSDVQEEKGFKYKFEVYEKND	854
hDHFR (Amino acid 2-187 of WT; K185E)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEEND	855
hDHFR (Amino acid 2-187 of WT; Y122I, A125F)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEFMNHPGHLKLFVTRIMQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	856
hDHFR (Amino acid 2-187 of WT; Q36F, N65F, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFFRMT TTSSVEGKQNLVIMGKKTWFSIPEKFRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	857
hDHFR (Amino acid 2-187 of WT; N127Y)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMYHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	858
hDHFR (Amino acid 2-187 of WT; H131R, E144G)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVYKEAMNHPGRLKLFVTRIMQDFGSDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	859
hDHFR (Amino acid 2-187 of WT; I17V)	VGSLNCIVAVSQNMGVGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLS RELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWI VGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDL EKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	860
hDHFR (Amino acid 2-187 of WT; Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	861
hDHFR (E162G, I176F)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVL SRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVW	862

	IVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEID LEKYKLLPGYPGVLSDVQEEKGFKYKFEVYEKND	
hDHFR (Amino acid 2-187 of WT; Q36K, Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFKRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLE KYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	863

[00126] 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.

[00127] 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.

[00128] 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.

[00129] 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. Stimulus

[00130] Biocircuits of the invention are triggered by one or more stimuli. Stimuli may be selected from a ligand, an externally added or endogenous metabolite, the presence or absence of a defined ligand, pH, temperature, light, ionic strength, radioactivity, cellular location, subject site, microenvironment, the presence or the concentration of one or more metal ions.

[00131] In some embodiments, the stimulus is a ligand. Ligands may be nucleic acid-based, protein-based, lipid based, organic, inorganic or any combination of the foregoing. In some embodiments, the ligand is selected from the group consisting of a protein, peptide, nucleic acid, lipid, lipid derivative, sterol, steroid, metabolite derivative and a small molecule. In some embodiments, the stimulus is a small molecule. In some embodiments, the small molecules are cell permeable. Ligands useful in the present invention include without limitation, any of those taught in Table 2 of copending commonly owned US serial number 62/320,684, 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. In some embodiments, the small molecules are FDA-approved, safe and orally administered.

[00132] In some embodiments, the ligand binds to dihydrofolate reductase. In some embodiments, the ligand binds to and inhibits dihydrofolate reductase function and is herein referred to as a dihydrofolate inhibitor.

[00133] In some embodiments, the ligand may be a selective inhibitor of human DHFR. Ligands of the invention may also be selective inhibitors of dihydrofolate reductases of bacteria and parasitic organisms such as *Pneumocystis spp.*, *Toxoplasma spp.*, *Trypanosoma spp.*, *Mycobacterium spp.*, and *Streptococcus spp.* Ligands specific to other DHFR may be modified to improve binding to human dihydrofolate reductase.

[00134] Examples of dihydrofolate inhibitors include, but are not limited to, Trimethoprim (TMP), Methotrexate (MTX), Pralatrexate, Piritrexim Pyrimethamine, Talotrexin, Chloroguanide, Pentamidine, Trimetrexate, aminopterin, C1 898 trihydrochloride, Pemetrexed Disodium, Raltitrexed, Sulfaguanidine, Folotyn, Iclaprim and Diaveridine. Other examples of DHFR inhibitors include BAL0030543, BAL0030544 and BAL0030545, developed by Basillea Pharmaceuticals; as well as WR 99210, and P218. Any of the inhibitors described by Zhang Q et al. (2015) Int J Antimicrob Agents. 2015 Aug; 46(2): 174–182 (the contents of which are incorporated herein by reference in their entirety). Some inhibitors contain bulky benzyl groups that dramatically diminish binding to human DHFR. In some embodiments, the inhibitors may be designed without bulky benzyl groups to improve TMP binding.

[00135] In some embodiments, ligands of the present invention may be polyglutamate or non polyglutamylatable. Like naturally occurring folates, polyglutamatable folates also contain a glutamic acid residue and therefore undergo intracellular polyglutamylation. In contrast, non-polyglutamatable antifolates are devoid of a glutamate residue and thus are not available for polyglutamylation. In some embodiments, polyglutamylatable ligands may be preferred to increase intracellular retention as they can no longer be exported out of the cell. In other embodiments, non polyglutamylatable ligands may be preferred to decrease intracellular retention.

[00136] In some embodiments, ligands of the present invention may include dihydrofolic acid or any of its derivatives that may bind to human DHFR. In some embodiments, the ligands of the present invention, may be 2,4, diaminohetrocyclic compounds. In some embodiments, the 4-oxo group in dihydrofolate may be modified to generate DHFR inhibitors. In one example, the 4 -oxo group may be replaced by 4-amino group. Various diamino heterocycles, including pteridines, quinazolines, pyridopyrimidines, pyrimidines, and triazines, may also be used as scaffolds to

develop DHFR inhibitors and may be used in the present invention. The crystal structure of DHFR in complex with known DHFR inhibitors may be utilized in the rational design of better DHFR ligands. The ligands used herein include a 2,4-diaminopyrimidine ring with a propargyl group linked to an optionally substituted aryl or heteroaryl ring (as described in US Patent No. US 8,426,432; the contents of which are incorporated herein by reference in their entirety).

[00137] In some embodiments, ligands include TMP- derived ligands containing portions of the ligand known to mediate binding to DHFR. Ligands may also be modified to reduce off-target binding to other folate metabolism enzymes and increase specific binding to DHFR.

3. Payloads: Immunotherapeutic agents

[00138] 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 a cytokine, a safety switch (e.g., a suicide gene), a regulatory switch, a chimeric antigen receptor, 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.

[00139] 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.

Cytokines, chemokines and other soluble factors

[00140] In accordance with the present invention, 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 several effector activities. For example, activated T cells produce a variety of cytokines for cytotoxic function to eliminate tumor cells.

[00141] 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. 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. 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.

[00142] In some embodiments, payloads of the present invention may be cytokine receptors, recombinant receptors, variants, analogs and derivatives thereof; or signal components of cytokines.

[00143] 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.

[00144] 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.

[00145] In one embodiment, the payload of the invention may comprise IL2. In one aspect, the effector module of the invention may be a DD-IL2 fusion polypeptide. The amino acid sequences corresponding to DD-IL2 and its components are listed in the Table 4. The amino acid sequences in Table 4 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 4: DD-IL2 construct sequences

Description	Amino Acid Sequence	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO/ Sequence
IL2 signal sequence	MYRMQLLSCIALSLALVTNS	49	55-56, 117-118
Linker	EFSTEF	50	57
Linker	MH	-	ATGCAC
IL2	APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRM LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNF HLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFL NRWITFCQSIISTLT	51	58-59
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKVDS SRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRAKLTI SPDYAYGATGHPGIIPPHATLVFDVELLKPE	11	60, 878-882
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNKP VIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVKSV DEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHIDA EVEGDTHFPDYEPDDWESVFSEFHDADAQNSHSYCFEIL ERR	9	61, 869-874
OT-IL2-001 (IL2 Signal Sequence – Linker (EFSTEF)-FKBP (F36V, L106P) – Linker (MH) – IL2- stop)	MYRMQLLSCIALSLALVTNSEFSTEFGVQVETISPGDGR TFPKRGQTCVVHYTGMLEDGKKVDSSRDRNKPFKFML GKQEVIRGWEEGVAQMSVGQRAKLTISPDYAYGATGH PGIIPPHATLVFDVELLKPEMHAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHL QCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT	52	62
OT-IL2-002 (IL2 Signal Sequence - IL2- stop)	MYRMQLLSCIALSLALVTNSAPTSSSTKKTQLQLEHLLL DLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQ CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK GSETTFMCEYADETATIVEFLNRWITFCQSIISTLT	53	63
OT-IL2-003 (IL2 Signal Sequence - Linker (EFSTEF)-ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) – Linker (MH) – IL2- stop)	MYRMQLLSCIALSLALVTNSEFSTEFISLIAALAVDYVIG MENAMPWNLPADLAWFKRNTLNKPVIMGRHTWESIGR PLPGRKNIILSSQPGTDDRVTWVKSVDEAIAACGDVPEI MVIGGGRVIEQFLPKAQKLYLTHIDAEVEGDTHFPDYEP DDWESVFSEFHDADAQNSHSYCFEILERRMHAPTSSSTK KTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYM PKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDL ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFC QSIISTLT	54	64

[00146] In some aspects of the invention, an IL2 mutein may be used as a payload. As used herein, the term "mutein" is a construct, molecule or sequence of a mutation, change or alteration in a protein and hence is also known as a mutant, e.g., a protein mutant, mutein. Consequently, an "IL2 mutein" is an IL2 mutant. In some embodiments an IL2 mutein is a variant of wild type IL2 protein, where the wildtype IL2 consists of the amino acid sequence of SEQ ID NO. 51. In some aspects, it refers to an IL2 variant which binds to and activates only cells expressing IL2Rαβγ, but does not significantly bind to or activate cell expressing only IL2Rβγ. In some examples, an IL2 mutein may be an IL2 protein in which residues of IL2 responsible for binding to either IL2Rβ or IL2Rγ are substituted to abolish the interaction of IL2 with IL2Rβ or IL2Rγ. In other examples, an IL2 mutein may be an IL2 protein comprising mutations conferring high affinity for IL2Rα. An IL2 mutein may be an IL2 selective agonist ($IL2_{SA}$) which can preferentially activate the high affinity IL2 receptor (i.e., IL2Rαβγ) which is necessary to selectively activate T cells with respect to NK cells. In some embodiments, the IL2 mutein may be IL2 protein which preferentially binds to the lower affinity IL2Rβγ but with reduced affinity to CD25.

[00147] In some embodiments, IL2 muteins may be used to preferentially expand or stimulate Treg cells. As used herein "preferentially expand or stimulate Treg cells" means the IL2 muteins promote the proliferation, survival, activation and /or function of T regulatory cells.

[00148] Exemplary IL2 muteins may include, but are not limited to, N88R substitution (Shanafelt et al., *Nature Biotech.*, 2000, 18:1197-1202), an IL2 with a V91K substitution (e.g., US Patent publication NO. US20140286898); V91K substitution, C125A substitution, an IL2 with three mutations: V69A, N71R, Q74P; an IL2 mutein with high affinity for IL2Rα (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P); an IL2 mutein with high affinity for IL2Rα and reduced signaling activity (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D), and D20H, D20I, N88G, N88I, N88R, and Q126L substitutions as described in PCT application NO. 1999060128; the contents of each of which are incorporated herein by reference in their entirety. In other aspects, IL2 muteins may include those described in US Patent NOs. 4,518,584; 5,116,943; 5,206,344; 6,955,807; 7,105,653; 7,371,371; 7,803,361; 8,124,066; 8,349,311; 8,759,486; and 9,206,243; PCT patent publication NOs. WO2005086751 and WO2012088446; European Patent N.s.: EP0234599 and EP0200280 and Sim, G.C. et al. (2016) Cancer Immunol Res; 4(11):983-994; the contents of each of which are incorporated herein by reference in their entirety.

[00149] In some aspects, the IL2 mutein may be fused to a polypeptide that extends the serum half-life of the IL2 mutein, such as an IgG Fc fragment. Preferred Fc regions are derived from

human IgG, which includes IgG1, IgG2, IgG3, and IgG4. In other aspects, the payload of the invention may be an IL2 fusion protein comparing a second functional polypeptide. In a non-limiting example, an IL2 fusion protein may comprise an IL2 or IL2 mutein polypeptide fused with a pro-apoptotic Bcl-2 family polypeptide (such as Bad, Bik/Nbk, Bid, Bim/Bod, Hrk, Bak or Bax); such fusion protein may be capable of inhibiting cell survival, inhibiting cell proliferation, or enhancing cell death or apoptosis of a target cell expressing an IL2 receptor. Alternatively, an IL2 or IL2 mutein polypeptide may be fused with an anti-apoptotic Bcl-2 family polypeptide (such as Bcl-$_{XL}$, Bcl-w or Bcl-2). The fusion protein may be capable of enhancing cell survival, enhancing cell proliferation, or inhibiting cell death or apoptosis of a target cell expressing an IL2 receptor. See, e.g., US patent publication NOS. US2016/0229901.

[00150] In addition, the IL2 fusion protein may be a IL2-GMCSF fusion protein which can promote cell-cell interaction; therefore, enhances anti-cancer immune responses (Wen et al., *J. Translational Med.*, 2016, 14: 41).

Safety switch

[00151] In some embodiments, payloads of the present invention may comprise SRE regulated safety switches that can eliminate adoptively transferred cells in the case of severe toxicity, thereby mitigating the adverse effects of T cell therapy. Adoptively transferred T cells in immunotherapy may attack normal cells in response to normal tissue expression of TAA. Even on-tumor target activity of adoptively transferred T cells can result in toxicities such as tumor lysis syndrome, cytokine release syndrome and the related macrophage activation syndrome. Safety switches may be utilized to eliminate inappropriately activated adoptively transferred cells by induction of apoptosis or by immunosurveillance.

[00152] In some embodiments, payloads of the present invention may comprise inducible killer/suicide genes that acts as a safety switch. The killer/suicide gene when introduced into adoptively transferred immune cells, could control their alloreactivity. The killer/suicide gene may be an apoptotic gene (e.g., any Caspase gene) which allows conditional apoptosis of the transduced cells by administration of a non-therapeutic ligand of the SRE (e.g., DD).

[00153] In some embodiments, the payload of the present invention may be Caspase 9. In some instances, Caspase 9 may be modified to have low basal expression and lacking the caspase recruitment domain (CARD) (SEQ ID NOS. 26 and SEQ ID NOS. 28 of US Patent No. US9434935B2; the contents of which are incorporated by reference in their entirety).

[00154] In one embodiment, the payload of the present invention is a suicide gene system, iCasp9/Chemical induced dimerization (CID) system which consists of a polypeptide derived from the Caspase9 gene fused to a drug binding domain derived from the human FK506 protein.

Administration of bioinert, small molecule AP1903(rimiducid), induces cross linking of the drug binding domains and dimerization of the fusion protein and in turn the dimerization of Caspase 9. This results in the activation of downstream effector Caspase 3 and subsequent induction of cellular apoptosis (Straathof et al., *Blood*, 2005, 105: 4247–4254; incorporated herein by reference in its entirety). Preclinical trials using CART including an iCasp9 gene have shown effective elimination of CAR T cells *in vivo* in mouse models and demonstrate the potential efficacy of this approach. (Budde et al, *Plos One*, 2013, 8: e82742.10.1371; Hoyos et al., *Leukemia*, 2010; 24(6):1160-1170). In one embodiment, the payload of the invention may comprise Caspase 9. In one aspect, the effector module of the invention may be a DD-Caspase9 fusion polypeptide. The DD-Caspase 9 may comprise the amino acid sequences provided in Table 5. The amino acid sequences in Table 5 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence

Table 5: DD-Caspase 9 constructs

Description/ Construct ID	Amino acid sequence	Amino Acid SEQ ID NO.	Nucleic Acid SEQ ID NO./ Sequence
Caspase 9	DEADRRLLRRCRLRLVEELQVDQLWDALLSRELFRPH MIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFISCLE DTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPEIR KPEVLRPETPRPVDIGSGGFGDVGALESLRGNADLAYI LSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLRRR FSSLHFMVEVKGDLTAKKMVLALLELAQQDHGALDC CVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIVNIF NGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSPED ESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFVSY STFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDLQSL LLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS	65	81-82
Caspase delta CD	GVDGFGDVGALESLRGNADLAYILSMEPCGHCLIINNV NFCRESGLRTRTGSNIDCEKLRRRFSSLHFMVEVKGDL TAKKMVLALLELARQDHGALDCCVVVILSHGCQASHL QFPGAVYGTDGCPVSVEKIVNIFNGTSCPSLGGKPKLFF IQACGGEQKDHGFEVASTSPEDESPGSNPEPDATPFQE GLRTFDQLDAISSLPTPSDIFVSYSTFPGFVSWRDPKSGS WYVETLDDIFEQWAHSEDLQSLLLRVANAVSVKGIYK QMPGCFNFLRKKLFFKTS	66	83
Linker	VDYPYDVPDYALD	67	84
Linker	SGGGS	68	85, 69, 86
Linker	QLIGMLQGLMRDL	908	909
Linker	SG	-	AGCGGC
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKVD SSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRAK LTISPDYAYGATGHPGIIPPHATLVFDVELLKPE	11	60, 878-882
FKBP (F36V)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKVD SSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRAK LTISPDYAYGATGHPGIIPPHATLVFDVELLKLE	70	87

FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQGA KLTISPDYAYGATGHPGIIPPHATLVFDVELLELE	12	88, 883-889
ecDHFR (R12Y, Y100I)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYL THIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSH SYCFEILERR	8	89
ecDHFR (Amino acid 2-159 of WT) (R12Y, E129K)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVK SVDEAIAACGDVPEIMVIGGGRVYEQFLPKAQKLYLTH IDAEVEGDTHFPDYKPDDWESVFSEFHDADAQNSHSY CFEILERR	71	90
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVK SVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHI DAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHSYC FEILERR	9	61, 869-874
hDHFR (Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLV LSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDM VWIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	18	91
hDHFR (V75F, Y122I)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLF LSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDM VWIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	31	92
hDHFR (L94A, T147A)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLV LSRELKEPPQGAHFLSRSADDALKLTEQPELANKVDM VWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDAFF PEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	32	93
OT-CASP9-001 (Met – FKBP (F36V, L106P) – Linker (SGGGS) – Caspase 9 - stop)	MGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKK VDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQR AKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPESGG GSDEADRRLLRRCRLRLVEELQVDQLWDALLSRELFR PHMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFISC LEDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPE IRKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADLA YILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLR RRFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGAL DCCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIV NIFNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSP EDESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFV SYSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDL QSLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS*	72	94
OT-CASP9-002 (ecDHFR (R12Y, Y100I) – Linker (SGGGS) - Caspase 9 - stop)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYL THIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSH SYCFEILERRSGGGSDEADRRLLRRCRLRLVEELQVDQ LWDALLSRELFRPHMIEDIQRAGSGSRRDQARQLIIDLE TRGSQALPLFISCLEDTGQDMLASFLRTNRQAAKLSKP TLENLTPVVLRPEIRKPEVLRPETPRPVDIGSGGFGDVG ALESLRGNADLAYILSMEPCGHCLIINNVNFCRESGLRT RTGSNIDCEKLRRRFSSLHFMVEVKGDLTAKKMVLAL LELAQQDHGALDCCVVVILSHGCQASHLQFPGAVYGT DGCPVSVEKIVNIFNGTSCPSLGGKPKLFFIQACGGEQK DHGFEVASTSPEDESPGSNPEPDATPFQEGLRTFDQLD	73	95

	AISSLPTPSDIFVSYSTFPGFVSWRDPKSGSWYVETLDDI FEQWAHSEDLQSLLLRVANAVSVKGIYKQMPGCFNFL RKKLFFKTS*		
OT-CASP9-003 (hDHFR (Y122I) – Linker (SGGGS) - Caspase 9 - stop)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLV LSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDM VWIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKNDS GGGSDEADRRLLRRCRLRLVEELQVDQLWDALLSREL FRPHMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFI SCLEDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLR PEIRKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADL AYILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKL RRRFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGA LDCCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIV NIFNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSP EDESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFV SYSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDL QSLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS*	74	96
OT-CASP9-004 (hDHFR (V75F, Y122I) – Linker (SGGGS) - Caspase 9 - stop)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLF LSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDM VWIVGGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFP EIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKNDS GGGSDEADRRLLRRCRLRLVEELQVDQLWDALLSREL FRPHMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFI SCLEDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLR PEIRKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADL AYILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKL RRRFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGA LDCCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIV NIFNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSP EDESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFV SYSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDL QSLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS*	75	97
OT-CASP9-005 (hDHFR (L94A, T147A) – Linker (SGGGS) - Caspase 9 - stop)	MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQR MTTTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLV LSRELKEPPQGAHFLSRSADDALKLTEQPELANKVDM VWIVGGSSVYKEAMNHPGHLKLFVTRIMQDFESDAFF PEIDLEKYKLLPEYPGVLSDVQEEKGIKYKFEVYEKND SGGGSDEADRRLLRRCRLRLVEELQVDQLWDALLSRE LFRPHMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPL FISCLEDTGQDMLASFLRTNRQAAKLSKPTLENLTPVV LRPEIRKPEVLRPETPRPVDIGSGGFGDVGALESLRGNA DLAYILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCE KLRRRFSSLHFMVEVKGDLTAKKMVLALLELAQQDH GALDCCVVVILSHGCQASHLQFPGAVYGTDGCPVSVE KIVNIFNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVAS TSPEDESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSD IFVSYSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSE DLQSLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS *	76	98
OT-CASP9-006 (Met – Leu – Glu - FKBP (F36V) – Linker (SGGGS) - Caspase Delta CD – Linker	MLEGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGK KVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQ RAKLTISPDYAYGATGHPGIIPPHATLVFDVELLKLESG GGSGVDGFGDVGALESLRGNADLAYILSMEPCGHCLII NNVNFCRESGLRTRTGSNIDCEKLRRRFSSLHFMVEVK GDLTAKKMVLALLELARQDHGALDCCVVVILSHGCQ ASHLQFPGAVYGTDGCPVSVEKIVNIFNGTSCPSLGGK PKLFFIQACGGEQKDHGFEVASTSPEDESPGSNPEPDAT	77	99

(QLIGMLQG LMRDL) - stop)	PFQEGLRTFDQLDAISSLPTPSDIFVSYSTFPGFVSWRDP KSGSWYVETLDDIFEQWAHSEDLQSLLLRVANAVSVK GIYKQMPGCFNFLRKKLFFKTSQLIGMLQGLMRDL*		
OT-CASP9-007 (Met - Caspase 9 – Linker (SG) – FKBP (E31G, F36V, R71G, K105E) - stop)	MDEADRRLLRRCRLRLVEELQVDQLWDALLSRELFRP HMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFISCL EDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPEI RKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADLAY ILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLRR RFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGALD CCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIVNI FNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSPE DESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFVS YSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDLQ SLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTSSGG VQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKVDS SRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQGAKL TISPDYAYGATGHPGIIPPHATLVFDVELLELE*	78	100
OT-CASP9-008 (Met - Caspase 9 – Linker (SG) - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - stop	MDEADRRLLRRCRLRLVEELQVDQLWDALLSRELFRP HMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFISCL EDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPEI RKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADLAY ILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLRR RFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGALD CCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIVNI FNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSPE DESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFVS YSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDLQ SLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTSSGI SLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVK SVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHI DAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHSYC FEILERR*	79	101
OT-CASP9-009 (Met - Caspase 9 - ecDHFR (Amino acid 2-159 of WT) (R12Y, E129K) - stop)	MDEADRRLLRRCRLRLVEELQVDQLWDALLSRELFRP HMIEDIQRAGSGSRRDQARQLIIDLETRGSQALPLFISCL EDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPEI RKPEVLRPETPRPVDIGSGGFGDVGALESLRGNADLAY ILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLRR RFSSLHFMVEVKGDLTAKKMVLALLELAQQDHGALD CCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIVNI FNGTSCPSLGGKPKLFFIQACGGEQKDHGFEVASTSPE DESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFVS YSTFPGFVSWRDPKSGSWYVETLDDIFEQWAHSEDLQ SLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTSSGI SLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVK SVDEAIAACGDVPEIMVIGGGRVYEQFLPKAQKLYLTH IDAEVEGDTHFPDYKPDDWESVFSEFHDADAQNSHSY CFEILERR*	80	102

[00155] In some instances, the iCasp9/CID system has been shown to have a basal rate of dimerization even in the absence of rimiducid, resulting in unintended cell death. Regulating the expression levels of iCasp9/CID is critical for maximizing the efficacy of iCasp9/CID system. Biocircuits of the present invention and/or any of their components may be utilized in regulating or tuning the iCasp9/CID system to optimize its utility. Other examples of proteins used in

dimerization-induced apoptosis paradigm may include, but are not limited to Fas receptor, the death effector domain of Fas-associated protein, FADD, Caspase 1, Caspase 3, Caspase 7 and Caspase 8. (Belshaw P.J. et al, *Chem Biol.*, 996,3:731-738; MacCorkle R.A. et al, *Proc Natl Acad Sci,* 1998, 95:3655-3660; Spencer, D.M. et al., *Curr Biol.*1996; 6:839-847; the contents of each of which are incorporated herein by reference in their entirety).

[00156] In some embodiments, the safety switch of the present invention may comprise a metabolic enzyme, such as herpes simplex virus thymidine kinase (HSV-TK) and cytosine deaminase (CD). HSV-TK phosphorylates nucleoside analogs, including acyclovir and ganciclovir (GCV) to generate triphosphate form of nucleosides. When incorporated into DNA, it leads to chain termination and cell death. Unlike the mammalian thymidine kinase, HSV-TK is characterized by 1000-fold higher affinity to nucleoside analogs such as GCV, making it suitable for use as a suicide gene in mammalian cells. Cytosine deaminase (CD) can converts 5-fluorocytosine (5-FC) into the cytotoxic 5-fluorouracil (5-FU) (Tiraby et al., *FEMS* Lett., 1998, 167: 41–49).

[00157] In some embodiments, the safety switch of the present invention may comprise a CYP4B1 mutant (as suicide gene), which may be co-expressed in a CAR engineered T cells (Roellecker et al., *Gen Ther.*, 2016, May 19, doi: 10.1038/gt.2016.38.).

[00158] In some embodiments, the payload of the present invention may comprise a fusion construct that can induce cell death, for example, a polypeptide with the formula of St-R1-S1-Q-S2-R2, wherein the St is a stalk sequence, R1/2 and Q are different epitopes; and S1/2 are optional spacer sequences (See International patent publication NOS. WO2013153391; the content of which are incorporated herein by reference in their entirety).

[00159] In some embodiments, safety switch may be mediated by therapeutic antibodies which specifically bind to an antigen that is expressed in the plasma membrane of adoptively transferred cells. The antigen-antibody interaction allows cell removal after administration of a specific monoclonal antibody against the antigen. As non-limiting examples, payloads of the present invention may comprise the antigen and antibody pair used to mediate safety switch such as CD20 and anti-CD20 antibody (Griffioen et al., *Haematologica*, 2009, 94:1316–1320), a protein tag and anti-tag antibody (Kieback et al., *Natl. Acad. Sci. U.S.A.*, 2008, 105: 623–628), a compact suicide gene (RQR8) combining epitopes from CD34 (as a marker moiety) and CD20 (as a suicide moiety) which enables CD34 selection, cell tracking, as well as cell deletion after anti-CD20 monoclonal antibody administration (Philip et al., *Blood*, 2014, 124: 1277–1287); truncated human EGFR polypeptide and anti-EGFR monoclonal antibody (Wang et al., *Blood*, 2011, 118:1255–1263); and a compact polypeptide safety switch having a structural formula as

discussed in U.S Patent Application Publication NOS. US20150093401; the contents of each of which are incorporated herein by reference in their entirety.

Regulatory switch

[00160] The utility of adoptive cell therapy (ACT) has been limited by the high incidence of graft versus host disease (GVHD). GVHD occurs when adoptively transferred T cells elicit an immune response resulting in host tissue damage. Recognition of host antigens by the graft cells triggers a proinflammatory cytokine storm cascade that signifies acute GVHD. GVHD is characterized as an imbalance between the effector and the regulatory arms of the immune system. In some embodiments, the payloads of the present invention may be used as regulatory switches. As used herein "regulatory switch" refers proteins, which when expressed in target cells increase tolerance to the graft by enhancing the regulatory arm of the immune system.

[00161] In one embodiment, regulatory switches may include payloads that preferentially promote the expansion of regulatory T (Treg cells). Tregs are a distinct population of cells that are positively selected on high affinity ligands in the thymus and play an important role in the tolerance to self-antigens. In addition, T regs have also been shown to play a role in peripheral tolerance to foreign antigens. Since Tregs promote immune tolerance, expansion of Tregs with the compositions of the invention may be desirable to limit GVHD.

[00162] In some embodiments, the regulatory switch may include, but is not limited to T regs activation factors such NFκB, FOXO, nuclear receptor Nr4a, Retinoic acid receptor alpha, NFAT, AP-1 and SMAD. Such factors can result in the expression of Fork headbox P3 (FOXP3) in T cells resulting in the activation of the regulatory T cell program and the expansion of T cells.

[00163] In one embodiment, the regulatory switch may be FOXP3, a transcriptional regulator in T cells. A function of FOXP3 is to suppress the function of NFAT, which leads to the suppression of expression of many genes including IL2 and effector T-cell cytokines. FOXP3 acts also as a transcription activator for genes such as CD2S, Cytotoxic T-Lymphocyte Antigen Cytotoxic T-Lymphocyte Antigen 4 (CTLA4), glucocorticoid-induced TNF receptor family gene (GITR) and folate receptor 4. FOXP3 also inhibits the differentiation of IL17 producing helper T-cells (Th17) by antagonizing RORC (RAR related orphan receptor C). Isoforms of FOXP3 lacking exon2 (FOXP3 delta 2), or exon 7 (FOXP3 delta 7) may also be used as regulatory switches. In one aspect, the effector module of the invention may be a DD-FOXP3 fusion polypeptide. The DD-FOXP3 may comprise the amino acid sequences provided in Table 6. The amino acid sequences in Table 6 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 6: DD-FOXP3 constructs

Construct/ Description	Amino Acid sequence	Amino Acid SEQ ID NO.	Nucleic Acid SEQ ID NO.
Linker	SGGGS	68	85, 69, 86
Linker	SG	-	AGCGGC
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKKVD SSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQRAK LTISPDYAYGATGHPGIIPPHATLVFDVELLKPE	11	60, 878-882
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKKV DSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQGA KLTISPDYAYGATGHPGIIPPHATLVFDVELLELE	12	88, 883-889
ecDHFR (R12Y, Y100I)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYL THIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSH SYCFEILERR	8	89
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTLNK PVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTWVK SVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYLTHI DAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSHSYC FEILERR	9	61, 869-874
FOXP3 full length	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLPL VMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGP*	103	911
Amino Acid 2-431 of FOXP3 full length	PNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGAR GPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLPLV MVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAHAR TPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPPGI NVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSSY PLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEKG RAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGKM ALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPREAP DSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMRPP FTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRNH PATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEFR KKRSQRPSRCSNPTPGP	104	912
FOXP3 delta 2	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDA HARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLP PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQS SYPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDE KGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAG KMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPR EAPDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNM RPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFR	105	913

	NHPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELE FRKKRSQRPSRCSNPTPGP		
FOXP3 delta 2	PNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGAR GPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDA HARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLP PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQS SYPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDE KGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAG KMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPR EAPDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNM RPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFR NHPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELE FRKKRSQRPSRCSNPTPGP	106	914
OT-FOXP3-001 (FoxP3 - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLPL VMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGP*	107	193
OT-FOXP3-002 (FoxP3 Delta 2 - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDA HARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLP PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQS SYPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDE KGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAG KMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPR EAPDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNM RPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFR NHPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELE FRKKRSQRPSRCSNPTPGP*	108	194
OT-FOXP3-003 (Met - FKBP (F36V, L106P) - Linker (SGGGS) - Amino Acid 2-431 of FOXP3 full length - stop)	MGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKK VDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQR AKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPESGG GSPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLG ARGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLP LVMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGP*	109	195
OT-FOXP3-004 (ecDHFR (R12Y, Y100I) – Linker (SGGGS) - Amino Acid 2-431 of	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYL THIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSH SYCFEILERRSGGGSPNPRPGKPSAPSLALGPSPGASPS WRAAPKASDLLGARGPGGTFQGRDLRGGAHASSSSLN PMPPSQLQLPTLPLVMVAPSGARLGPLPHLQALLQDRP HFMHQLSTVDAHARTPVLQVHPLESPAMISLTPPTTAT GVFSLKARPGLPPGINVASLEWVSREPALLCTFPNPSAP	110	196

FOXP3 full length - stop)	RKDSTLSAVPQSSYPLLANGVCKWPGCEKVFEEPEDFL KHCQADHLLDEKGRAQCLLQREMVQSLEQQLVLEKE KLSAMQAHLAGKMALTKASSVASSDKGSCCIVAAGSQ GPVVPAWSGPREAPDSLFAVRRHLWGSHGNSTFPEFL HNMDYFKFHNMRPPFTYATLIRWAILEAPEKQRTLNEI YHWFTRMFAFFRNHPATWKNAIRHNLSLHKCFVRVES EKGAVWTVDELEFRKKRSQRPSRCSNPTPGP*		
OT-FOXP3-005 (FoxP3 – Linker (SG) - FKBP (E31G, F36V, R71G, K105E) - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLPL VMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGPSGGVQVETISPGDGRTFPKRG QTCVVHYTGMLGDGKKVDSSRDRNKPFKFMLGKQEV IRGWEEGVAQMSVGQGAKLTISPDYAYGATGHPGIIPP HATLVFDVELLELE*	111	197
OT-FOXP3-006 (FoxP3 – Linker (SG) - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLPTLPL VMVAPSGARLGPLPHLQALLQDRPHFMHQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGPSGISLIAALAVDYVIGMENA MPWNLPADLAWFKRNTLNKPVIMGRHTWESIGRPLPG RKNIILSSQPGTDDRVTWVKSVDEAIAACGDVPEIMVI GGGRVIEQFLPKAQKLYLTHIDAEVEGDTHFPDYEPDD WESVFSEFHDADAQNSHSYCFEILERR*	112	198
OT-FOXP3-007 (Met - FKBP (F36V, L106P) – Linker (SG) - Amino Acid 2-396 of FOXP3 delta 2 - stop)	MGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKK VDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQR AKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPESGP NPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGARG PGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDAH ARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLPP GINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSS YPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDEK GRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAGK MALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPRE APDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMR PPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFRN HPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELEF RKKRSQRPSRCSNPTPGP*	113	199
OT-FOXP3-008 (ecDHFR (R12Y, Y100I) – Linker (SG) - Amino Acid 2-396 of	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNTL NKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVTW VKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQKLYL THIDAEVEGDTHFPDYEPDDWESVFSEFHDADAQNSH SYCFEILERRSGPNPRPGKPSAPSLALGPSPGASPSWRA APKASDLLGARGPGGTFQGRDLRGGAHASSSSLNPMP PSQLQLSTVDAHARTPVLQVHPLESPAMISLTPPTTATG VFSLKARPGLPPGINVASLEWVSREPALLCTFPNPSAPR	114	200

FOXP3 delta 2 - stop)	KDSTLSAVPQSSYPLLANGVCKWPGCEKVFEEPEDFLK HCQADHLLDEKGRAQCLLQREMVQSLEQQLVLEKEK LSAMQAHLAGKMALTKASSVASSDKGSCCIVAAGSQG PVVPAWSGPREAPDSLFAVRRHLWGSHGNSTFPEFLH NMDYFKFHNMRPPFTYATLIRWAILEAPEKQRTLNEIY HWFTRMFAFFRNHPATWKNAIRHNLSLHKCFVRVESE KGAVWTVDELEFRKKRSQRPSRCSNPTPGP*		
OT-FOXP3-009 (FoxP3 Delta 2-Linker (SG) - FKBP (E31G, F36V, R71G, K105E) - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDA HARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLP PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQS SYPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDE KGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAG KMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPR EAPDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNM RPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFR NHPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELE FRKKRSQRPSRCSNPTPGPSGGVQVETISPGDGRTFPKR GQTCVVHYTGMLGDGKKVDSSRDRNKPFKFMLGKQE VIRGWEEGVAQMSVGQGAKLTISPDYAYGATGHPGIIP PHATLVFDVELLELE*	115	201
OT-FOXP3-010 (FoxP3 Delta 2-Linker (SG) - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - stop)	MPNPRPGKPSAPSLALGPSPGASPSWRAAPKASDLLGA RGPGGTFQGRDLRGGAHASSSSLNPMPPSQLQLSTVDA HARTPVLQVHPLESPAMISLTPPTTATGVFSLKARPGLP PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQS SYPLLANGVCKWPGCEKVFEEPEDFLKHCQADHLLDE KGRAQCLLQREMVQSLEQQLVLEKEKLSAMQAHLAG KMALTKASSVASSDKGSCCIVAAGSQGPVVPAWSGPR EAPDSLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNM RPPFTYATLIRWAILEAPEKQRTLNEIYHWFTRMFAFFR NHPATWKNAIRHNLSLHKCFVRVESEKGAVWTVDELE FRKKRSQRPSRCSNPTPGPSGISLIAALAVDYVIGMENA MPWNLPADLAWFKRNTLNKPVIMGRHTWESIGRPLPG RKNIILSSQPGTDDRVTWVKSVDEAIAACGDVPEIMVI GGGRVIEQFLPKAQKLYLTHIDAEVEGDTHFPDYEPDD WESVFSEFHDADAQNSHSYCFEILERR*	116	202

Antibodies

[00164] In some embodiments, antibodies, fragments and variants thereof are payloads of the present invention.

[00165] 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 which are incorporated herein by reference in their entirety.

Antibody fragments and variants

[00166] 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.

[00167] 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.

[00168] 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).

[00169] 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).

[00170] 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).

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] 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.

[00180] 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.

[00181] 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.

[00182] 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.

[00183] 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.

[00184] 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.

[00185] 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).

[00186] 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).

[00187] 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).

[00188] 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.

[00189] 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.

[00190] 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.

[00191] 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).

[00192] 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.

[00193] 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.

[00194] 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

[00195] 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.

[00196] 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.

[00197] 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

[00198] 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.

[00199] 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.

[00200] In one embodiment, the antigen may be GD2 ganglioside. In one embodiment, payloads of the present invention may be antibodies, fragments and variants thereof which are

specific to GD2 antigen. Gangliosides expressed on the tumor cell surface can be targets for cancer immunotherapy. GD2 is a disialoganglioside with a molecular formula of C74H134N4032. Gangliosides are acidic glycosphingolipids found on the outer surface of most cell membranes. They are ideal targets for immunotherapy because of the high antigen density, lack of modulation, relative homogeneity in many tumors and the possibility of up regulation by cytokines. Many tumors have abnormal glycolipid composition and structure. GD2 has been found in a wide spectrum of human tumors, including those of neuroectodermal or epithelial origin, virtually all melanomas, and approximately 50% of tumor samples from osteosarcoma and soft tissue sarcoma. Antibodies with high affinity for GD2 include, but not limited to 1B7, 2H12, 1G2, 1E9, 1H3, 2F5, 2F7, 31F9, 31F9V2, 32E2, chl4.18, hul4.18, 3F8, 8B6, 4B5, 1A7, A1G4, GD2 mimotopes, hul4.18K322A, 5F11, 3G6, 14g2a, and 14.18. In one embodiment, the GD antibody is the 14g2a antibody (Mujoo K., et al. (1989) Cancer Res. 1;49(11):2857-61; the contents of which are incorporated herein by reference in its entirety). Any of the GD2 antibodies described in Long A.H. et al. (2015) Nat Med. 21(6):581-90; the contents of which are incorporated by reference in their entirety).

[00201] In one embodiment, the antigen is HER2 antigen. In one embodiment, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to HER2 antigen. HER2 is the oncogene product of human epidermal cell growth factor receptor 2 related oncogenes and is a transmembrane receptor protein having a molecular weight of 185 kDa and having a tyrosine kinase domain. HER2 is a member of the EGFR family consisting of HER1 (EGFR, ERBB1), HER2 (neu, ERBB-2), HER2 (ErbB-3), and Her4 (ErbB-4) and is known to be autophosphorylated at intracellular tyrosine residues by its homodimer formation or heterodimer formation with another EGFR receptor HER1, HER3, HER4 and is activated in this manner. Thereby playing an important role in cell growth, differentiation, and survival in normal cells and tumor cells. In some embodiments, HER2 antibodies useful in the present invention may include 3B5 (from Oncogene Science/BAYER), 2C4 (ATCC HB-12697), 7C2 (ATCC HB-12215), ApoB17F/ocHER2, 8A4 (ATCC PTA-4565), A10A12 (ATCC PTA- 4566), 9G6 , 7H4, AlOE9, A12D6, A6B12, A10E11, B3G4, A5C7, 13A11, 11C11, 13E11, Her2Bi (OKT3 x 9184), Her2Bi (OKT3 x Herc), 7F3 (ATCC HB-12216), huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-6, huMAb4D5-7, 520C9, CB-11 (from Novocastra Laboratories), NCLB12 (from Novocastra Laboratories), humanized 2C4 mutant 560, humanized 2C4 mutant 561, humanized 2C4 mutant 562, humanized 2C4 mutant 568, humanized 2C4 mutant 569, humanized 2C4 mutant 570, humanized 2C4 mutant 571, humanized 2C4 mutant 56869, 3E8, 3H4, Cl 11 (NeoMarkers), HER-81, 452F2, 736G9, 741F8, 758G5, 761B10 , anti-

p185HER2/FcγRIII (CD16) , anti-CD3/anti-p185HER2 , Hu4D5-8 and variants, 4D5-H, CB11 (from Ventana Medical Scientific Instruments), 6E9, 2H11, 5B8, 7D3, HER50, HER66, HER70, scFv C6.5, scFv C6ML3-9 (ML3.9 or C6ML3.9), scFv C6MH3-B1 (B1 or C6MH3.B1), scFv C6-B1D2, (B1D2 or C6MH3-B1D2), ALM, L87, N28 , N12 , MGr6 , 9GG.10 (Neomarkers), MGFc-5 (V379M), MGFc-9 (F243I, V379L), MGFc-10 (K288N, A330S, P396L), MGFc-13 (K334E, T359N, T366S), MGFc-27 (G316D, A378V, D399E), MGFc-37 (K248M), MGFc-39 (E293V Q295E, A327T), MGFc-38 (K392T, P396L), MGFc-41 (H268N, P396L), MGFc-23 (K334E, R292L), MGFc-44, MGFc-45, MDX-210, 17.6.4 , HER2-PY1248, MAb74, FRP5, TAb250, HER-81, PN2A, mAb 191924 (R&D systems), IDMI, scFv23, Ab-3, Ab-5 , 2502A, Rexomun, MAB-1129 (R&D systems), and MM-111. In one embodiment, antibodies with high affinity may be derived from any of the HER2 antibody heavy and light chain variables described in Table 7.

[00202] In one embodiment of the present invention, the antigen is CD33. In one embodiment, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to CD33 antigen. Acute myeloid leukemia (AML) is the second most common acute leukemia in the United States. The commonly applied therapy of leukemic disease includes irradiation and/or chemotherapy. However, very often 65-80% of patients receiving treatment relapse because the cells that survived the chemotherapy are enriched in AML leukemia stem cells (AML-LSCs), and constitute a reservoir of cells capable of re-expanding and causing a relapse. AML-LSCs express a characteristic set of cell surface antigens including among other CD33. CD33 (Sialic acid binding Ig-like lectin 3) or SIGLEC3(UNIPROT ID: P20138) is a transmembrane receptor expressed on cells of myeloid lineage. It is usually considered myeloid specific, but it can also be found on some lymphoid cells. It binds to sialic acid, therefore is a member of the SIGLEC family of lectins. Exemplary antibodies targeting CD33 may include, but are not limited to M195, M2H12, DRB2, My 9-6. In one embodiment, the antibody is derived from My9.6. In some embodiments, antibodies with high affinity may be derived from any of the CD33 antibody heavy and light chain variables described in Table 7.

[00203] In one embodiment, the antigen of the present invention is a BCMA (B-cell maturation antigen), also referred to as the CD269. In one embodiment, payloads of the present invention may be antibodies, fragments and variants thereof which are specific to BCMA antigen. BCMA antigen (UNIPROT ID: Q02223) is encoded by the gene, TNFRS17. BCMA is a member of the TNF receptor super family. It binds to B cell activating factor (BAFF) and a proliferation inducing ligand (APRIL). Among non-malignant cells, BCMA has been reported to be expressed mostly by plasma cells and subsets of mature B cells, but not T cells and NK cells. Therefore,

BCMA represents a suitable therapeutic candidate in the treatment of multiple myeloma. Exemplary antibodies targeting BCMA include, but are not limited to BCMA 50, BCMA30, C11D5.3 and C13F12.1 In one embodiment, the antibody is derived from C11D5.3. In some embodiments, antibodies with high affinity may be derived from any of the BCMA antibody heavy and light chain variables described in Table 7.

[00204] In one embodiment, the antigen of the present invention is a CD276 (also known as B7-H3). In one embodiment, payloads of the present invention may be antibodies, fragment, and variants thereof which are specific to CD276. CD276 is expressed in a variety of human tumors, including pediatric solid tumors and adult carcinomas. Any of the CD276 antibodies taught in International Patent publications WO2017044699 and WO2014160627 (the contents of which are incorporated herein by reference in their entirety), may be useful in the present invention. In some embodiments, antibodies with high affinity may be derived from any of the CD276 antibody heavy and light chain variables described in Table 7.

[00205] In one embodiment, the antigen of the present invention is a ALK protein. The developmentally-regulated cell surface receptor tyrosine kinase, ALK is known to be expressed as a tumor associated antigen as a fusion protein resulting from a chromosomal translocation. Cancer associated ALK was first described as a 2;5 translocation associated with nucleophosphomin (NPM) in anaplastic large cell leukemia. The fusion protein is composed of intracellular component of NPM fused to ALK. In some embodiments, the ALK antigen may be the extracellular portion of the protein. Any of the antibodies, fragment and variants specific to ALK may be useful in the present invention. In one embodiment, the ALK antibodies described in the International Patent Publication, WO2015069922 (the contents of which are incorporated by reference herein in its entirety). In some embodiments, antibodies with high affinity may be derived from any of the ALK antibody heavy and light chain variables described in Table 7.

[00206] In one embodiment, the antigen of the present invention is a CD22 antigen. In one embodiment, payloads of the present invention may be antibodies, fragment, and variants thereof which are specific to CD22. CD22 is a lineage restricted B cell antigen belonging to the immunoglobulin (Ig) superfamily. CD22 is expressed in 60-70% of B cell lymphomas and leukemias (e.g. B-chronic lymphocytic leukemia, hairy cell leukemia, acute lymphocytic leukemia (ALL) and Burkit's lymphoma) and is not present on the cell surface in early stages of B cell development or on to stem cells. In some embodiments, the antibodies, fragments, and variants thereof may be any of those taught in International Patent Publications, WO2016149578, WO2014065961, and WO2013059593A1(the contents of each of which are incorporated by reference in its entirety). In some embodiments, antibodies with high affinity

may be derived from any of the CD22 antibody heavy and light chain variables described in Table 7.

[00207] In some embodiments, the payloads of the present invention may include an antigen binding region comprising variable heavy chain and variable light chains with the amino acid sequences selected from those in Table 7.

Table 7: Variable Heavy and Light Chain Sequences

Target	Description and Clone name	Source	Antibody chain	SEQ ID NO.
ALK	ALK15 VH	SEQ ID NO. 1 in WO2015069922	VH	242
ALK	ALK48 VH	SEQ ID NO. 3 in WO2015069922	VH	243
ALK	ALK53 VH	SEQ ID NO. 5 in WO2015069922	VH	244
ALK	ALK58 VH	SEQ ID NO. 7 in WO2015069922	VH	245
ALK	humanized ALK15 VH	SEQ ID NO. 9 in WO2015069922	VH	246
ALK	humanized ALK48 VH	SEQ ID NO. 11 in WO2015069922	VH	247
ALK	humanized ALK53 VH	SEQ ID NO. 13 in WO2015069922	VH	248
ALK	humanized ALK58 VH	SEQ ID NO. 15 in WO2015069922	VH	249
ALK	ALK15 VL	SEQ ID NO. 2 in WO2015069922	VL	250
ALK	ALK48 VL	SEQ ID NO. 4 in WO2015069922	VL	251
ALK	ALK53 VL	SEQ ID NO. 6 in WO2015069922	VL	252
ALK	ALK58 VL	SEQ ID NO. 8 in WO2015069922	VL	253
ALK	humanized ALK15 VL	SEQ ID NO. 10 in WO2015069922	VL	254
ALK	humanized ALK48 VL	SEQ ID NO. 12 in WO2015069922	VL	255
ALK	humanized ALK53 VL	SEQ ID NO. 14 in WO2015069922	VL	256
ALK	humanized ALK58 VL	SEQ ID NO. 16 in WO2015069922	VL	257
CD22	CD22 VL	SEQ ID NO. 14 in WO2016149578	VL	258
CD22	CD22 (HA22 or BL22) VL	SEQ ID NO. 1 in WO2013059593	VL	259
CD22	CD22 VH	SEQ ID NO. 13 in WO2016149578	VH	260
CD22	CD22 (HA22 or BL22) VH	SEQ ID NO. 3 in WO2013059593	VH	261
CD22	CD22 (HA22 or BL22) VH	SEQ ID NO. 4 in WO2013059593	VH	262
CD276	CD276 VH	SEQ ID NO. 7 in WO2017044699	VH	263
CD276	CD276 VH (CD276.6 (m856))	SEQ ID NO. 7 in WO2014160627	VH	264
CD276	CD276 VH (CD276.1 (m851))	SEQ ID NO. 17 in WO2014160627	VH	265

CD276	CD276 VH (CD276.17 (m8517))	SEQ ID NO. 26 in WO2014160627	VH	266
CD276	CD276 VL	SEQ ID NO. 8 in WO2017044699	VL	267
CD276	CD276 VL (CD276.6 (m856))	SEQ ID NO. 8 in WO2014160627	VL	268
CD276	CD276 VL (CD276.1 (m851))	SEQ ID NO. 18 in WO2014160627	VL	269
CD276	CD276 VL (CD276.17 (m8517))	SEQ ID NO. 27 in WO2014160627	VL	270
GD2	3F8 heavy chain variable	SEQ ID No. 1 in WO2011160119	VH	271
GD2	3F8 light chain variable	SEQ ID No. 2 in WO2011160119	VL	272
GD2	3F8 heavy chain variable	SEQ ID No. 3 in WO2011160119	VH	273
GD2	humanized 3F8 heavy chain variable	SEQ ID No. 4 in WO2011160119	VH	274
GD2	humanized 3F8 light chain variable	SEQ ID No. 5 in WO2011160119	VL	275
GD2	humanized 3F8 heavy chain 2 variable	SEQ ID No. 6 in WO2011160119	VH	276
GD2	humanized 3F8 light chain 2 variable	SEQ ID No. 7 in WO2011160119	VL	277
GD2	humanized 3F8 heavy chain variable	SEQ ID No. 8 in WO2011160119	VH	278
GD2	Human GD2 heavy chain variable	SEQ ID No. 16 in WO2010002822A1	VH	279
GD2	Human GD2 light chain variable	SEQ ID No. 32 in WO2010002822A1	VL	280
GD2	chimeric Ch3F8 heavy chain-gamma 1	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VH	281
GD2	chimeric Ch3F8 light chain-kappa	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VL	282
GD2	humanized Hu3F8 heavy chain-gamma1	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VH	283
GD2	humanized Hu3F8 light chain-kappa	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VL	284
GD2	Chimeric Ch3F8 heavy chain-gamma4	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VH	285
GD2	humanized Hu3F8 heavy chain-gamma4	Cheung et al., Oncoimmunology, 2012, 1(4): 477-486	VL	286
GD2	GD2 VH	SEQ ID NO. 17 in WO2016134284	VH	287
GD2	GD2 VL	SEQ ID NO. 18 in WO2016134285	VL	288
GD2	Murine KM666 VH (heavy chain variable region) sequence	SEQ ID NO. 9 in WO2015132604	VH	289

GD2	Humanized KM666 VH sequence	SEQ ID NO. 10 in WO2015132604	VH	290
GD2	Murine KM666 VL (light chain variable region) sequence	SEQ ID NO. 11 in WO2015132604	VL	291
GD2	Humanized KM666 VL sequence	SEQ ID NO. 12 in WO2015132604	VL	292
GD2	GD2 VL	SEQ ID NO. 1 in US20040203100	VL	293
GD2	GD2 VH	SEQ ID NO. 2 in US20040203100	VH	294
GD2	Murine KM666 VH (heavy chain variable region) sequence	SEQ ID NO. 9 in US20170066838	VH	295
GD2	Humanized KM666 VH sequence	SEQ ID NO. 10 in US20170066838	VH	296
GD2	Murine KM666 VL (light chain variable region) sequence	SEQ ID NO. 11 in US20170066838	VL	297
GD2	Humanized KM666 VL sequence	SEQ ID NO. 12 in US20170066838	VL	298
GD2	GD2 VL	SEQ ID NO.3 in US20160304620	VL	299
GD2	GD2 VH	SEQ ID NO. 4 in US20160304620	VH	300
GD2	GD2 VH	SEQ ID NO. 2 in US20150353645	VH	301
GD2	GD2 VL	SEQ ID NO. 4 in US20150353645	VL	302
GD2	GD2 VH	SEQ ID NO. 6 in US20150353645	VH	303
GD2	GD2 VL	SEQ ID NO. 8 in US20150353645	VL	304
GD2	GD2 VH	SEQ ID NO. 10 in US20150353645	VH	305
GD2	GD2 VL	SEQ ID NO. 12 in US20150353645	VL	306
GD2	GD2 VH	SEQ ID NO. 14 in US20150353645	VH	307
GD2	GD2 VL	SEQ ID NO. 16 in US20150353645	VL	308
GD2	GD2 VH	SEQ ID NO. 18 in US20150353645	VH	309
GD2	GD2 VL	SEQ ID NO. 20 in US20150353645	VL	310
GD2	GD2 VH	SEQ ID NO. 22 in US20150353645	VH	311
GD2	GD2 VL	SEQ ID NO. 24 in US20150353645	VL	312
GD2	GD2 VH	SEQ ID NO. 26 in US20150353645	VH	313
GD2	GD2 VL	SEQ ID NO. 28 in US20150353645	VL	314
GD2	GD2 VH	SEQ ID NO. 30 in US20150353645	VH	315

GD2	GD2 VL	SEQ ID NO. 32 in US20150353645	VL	316
GD2	GD2 VH	SEQ ID NO. 34 in US20150353645	VH	317
GD2	GD2 VH	SEQ ID NO. 36 in US20150353645	VH	318
GD2	GD2 VL	SEQ ID NO. 38 in US20150353645	VL	319
GD2	GD2 VH	SEQ ID NO. 40 in US20150353645	VH	320
GD2	GD2 VL	SEQ ID NO. 42 in US20150353645	VL	321
GD2	GD2 VL	SEQ ID NO. 3 in US20150139942	VL	322
GD2	GD2 VH	SEQ ID NO. 4 in US20150139942	VH	323
GD2	GD2 VL	SEQ ID NO. 7 in US20150139942	VL	324
GD2	GD2 VH	SEQ ID NO. 8 in US20150139942	VH	325
GD2	GD2 VH	SEQ ID NO. 16 in US20130287691	VH	326
GD2	GD2 VL	SEQ ID NO. 32 in US20130287691	VL	327
GD2	GD2 VH	SEQ ID NO. 40 in US20130287691	VH	328
GD2	GD2 VL	SEQ ID NO. 42 in US20130287691	VL	329
GD2	GD2 VL	SEQ ID NO. 3 in US20140134162	VL	330
GD2	GD2 VH	SEQ ID NO. 4 in US20140134162	VH	331
GD2	GD2 VH	SEQ ID NO. 20 in WO2017055385	VH	332
GD2	GD2 VL	SEQ ID NO. 20 in WO2017055385	VL	333
GD2	GD2 VH	SEQ ID NO. 3 in WO2013189516	VH	334
GD2	GD2 VL	SEQ ID NO. 4 in WO2013189516	VL	335
GD2-0-acetylated	KM8B6 GD2-0-acetylated heavy chain variable	SEQ ID No. 1 in WO2008043777	VH	336
GD2-0-acetylated	KM8B6 GD2-0-acetylated light chain variable	SEQ ID No. 2 in WO2008043777	VL	337
GD2-0-acetylated	O-acetylated-GD2 ganglioside light chain variable region	SEQ ID No. 6 in WO2015067375	VL	338
GD2-0-acetylated	O-acetylated-GD2 ganglioside heavy chain variable region	SEQ ID No. 7 in WO2015067375	VH	339
GD2-0-acetylated	GD2 VL	SEQ ID NO.7 in US20160068608	VL	340

GD2-0-acetylated	GD2 VH	SEQ ID NO.8 in US20160068608	VH	341
GD2-0-acetylated	GD2 VL (8B6)	SEQ ID NO. 7 in WO2014177271A1	VL	342
GD2-0-acetylated	GD2 VH (8B6)	SEQ ID NO. 8 in WO2014177271A1	VH	343
GD2-0-acetylated	GD2 VL	SEQ ID NO. 9 in WO2014177271A1	VL	344
GD2-0-acetylated	GD2 VH	SEQ ID NO. 10 in WO2014177271A1	VH	345
Gangliosides (including GD2)	GMab1-VH	SEQ ID No. 11 in WO2012071216	VH	346
Gangliosides (including GD2)	GMab1-VH	SEQ ID No. 12 in WO2012071216	VL	347
Gangliosides (including GD2)	GMab1-VL	SEQ ID No. 13 in WO2012071216	VH	348
Gangliosides (including GD2)	GMab2-VH	SEQ ID No. 14 in WO2012071216	VL	349
CD33	Anti CD33 VH (Clone M195)	SEQ ID NO. 11 in WO2015150526	VH	350
CD33	Anti CD33 VL (Clone M195)	SEQ ID NO. 12 in WO2015150526	VL	351
CD33	Anti CD33 VH (Clone M2H12)	SEQ ID NO. 13 in WO2015150526	VH	352
CD33	Anti CD33 VL (Clone M2H12)	SEQ ID NO. 14 in WO2015150526	VL	353
CD33	Anti CD33 VH (Clone DRB2)	SEQ ID NO. 15 in WO2015150526	VH	354
CD33	Anti CD33 VL (Clone DRB2)	SEQ ID NO. 16 in WO2015150526	VL	355
CD33	Anti CD33 VH (Clone My9-6)	SEQ ID NO. 17 in WO2015150526	VH	356
CD33	Anti CD33 VL (Clone My9-6)	SEQ ID NO. 18 in WO2015150526	VL	357
BCMA	BCMA VH (Clone BCMA-50)	SEQ ID NO. 11 in WO2015158671	VH	358
BCMA	BCMA VL (Clone BCMA-50)	SEQ ID NO. 12 in WO2015158672	VL	359
BCMA	BCMA VH (Clone BCMA-30)	SEQ ID NO. 13 in WO2015158673	VH	360
BCMA	BCMA VL (Clone BCMA-30)	SEQ ID NO. 14 in WO2015158674	VL	361
BCMA	BCMA VH (Clone C11D5.3)	SEQ ID NO. 15 in WO2015158675	VH	362

BCMA	BCMA VL (Clone C11D5.3)	SEQ ID NO. 16 in WO2015158676	VL	363
BCMA	BCMA VH (Clone C13F12.1)	SEQ ID NO. 17 in WO2015158677	VH	364
BCMA	BCMA VL (Clone C13F12.1)	SEQ ID NO. 18 in WO2015158678	VL	365
Her2	Trastuzumab (Herceptin)	SEQ ID NO. 1 in WO2017093844	VH	366
Her2	Trastuzumab (Herceptin)	SEQ ID NO. 7 in WO2017093844	VL	367
Her2	huMAb4D5-5	SEQ ID NO. 1 in US 8,075,890	VL	368
Her2	huMAb4D5-5	SEQ ID NO. 2 in US 8,075,890	VH	369
Her2	a consensus antibody variable domain	SEQ ID NO. 3 in US 8,075,890	VL	370
Her2	a consensus antibody variable domain	SEQ ID NO. 4 in US 8,075,890	VH	371
Her2	muMAb4D5	SEQ ID NO. 5 in US 8,075,890	VL	372
Her2	muMAb4D5	SEQ ID NO. 6 in US 8,075,890	VH	373
Her2	N29	No SEQ ID in WO1993003741	VH	374
Her2	N29	No SEQ ID in WO1993003741	VL	375
Her2	2C4	SEQ ID NO. 1 in US 7,981,418	VL	376
Her2	2C4	SEQ ID NO. 2 in US 7,981,418	VH	377
Her2	variant 574/Pertuzumab	SEQ ID NO. 3 in US 7,981,418	VL	378
Her2	variant 574/Pertuzumab	SEQ ID NO. 4 in US 7,981,418	VH	379
Her2	human VL consensus (hum. kappa.1, light kappa subgroup 1)	SEQ ID NO. 5 in US 7,981,418	VL	380
Her2	human VH consensus (humIII, heavy subgroup III)	SEQ ID NO. 6 in US 7,981,418	VH	381
Her2	Pertuzumab	SEQ ID NO. 13 in US 7,981,418	VL	382
Her2	Pertuzumab	SEQ ID NO. 14 in US 7,981,418	VH	383
Her2	trastuzumab/humMAb4 D5-8	SEQ ID NO. 15 in US 7,981,418	VL	384
Her2	trastuzumab/humMAb4 D5-8	SEQ ID NO. 16 in US 7,981,418	VH	385
Her2	a variant Pertuzumab light chain sequence	SEQ ID NO. 17 in US 7,981,418	VL	386
Her2	a variant Pertuzumab heavy chain sequence	SEQ ID NO. 18 in US 7,981,418	VH	387

Her2	3. F2 monoclonal antibody	SEQ ID NO. 2 in WO2001009187	VH	388
Her2	3. F2 monoclonal antibody	SEQ ID NO. 4 in WO2001009187	VL	389
Her2	1. D2 monoclonal antibody	SEQ ID NO. 6 in WO2001009187	VH	390
Her2	1. D2 monoclonal antibody	SEQ ID NO. 8 in WO2001009187	VL	391
Her2	2. E8 monoclonal antibody	SEQ ID NO. 10 in WO2001009187	VH	392
Her2	2. E8 monoclonal antibody	SEQ ID NO. 12 in WO2001009187	VL	393
Her2	2C4	SEQ ID NO. 4 in US 7,097,840	VL	394
Her2	variant 574/Pertuzumab	SEQ ID NO. 5 in US 7,097,840	VL	395
Her2	human VL subgroup	SEQ ID NO. 6 in US 7,097,840	VL	396
Her2	4D5	SEQ ID NO. 14 in WO2003068801	VH	397
Her2	Hu4D5-8	SEQ ID NO. 1 in WO2003087131	VL	398
Her2	rhuMAb	SEQ ID NO. 50 in US20040254108	VH	399
Her2	rhuMAb	SEQ ID NO. 52 in US20040254108	VL	400
Her2	her2VHCH - SM5-1 VH; human kappa chain constant (CH)	SEQ ID NO. 54 in US20040254108	VH	401
Her2	her2VLCL - SM5-1 VL; human kappa chain constant (CL)	SEQ ID NO. 56 in US20040254108	VL	402
Her2	her2VH/Fc/FL-- rhuMAb VH; IgG1 Fc; Flt3 ligand extracellular region (hFLex)	SEQ ID NO. 58 in US20040254108	VH	403
Her2	her2VH/Fc/Link/FL -- rhuMAb; IgG1 Fc; linker; Flt3 ligand extracellular region (hFLex)	SEQ ID NO. 60 in US20040254108	VH	404
Her2	Herceptin Fab	SEQ ID NO. 9 in US20050260711A1	VL	405
Her2	Herceptin Fab	SEQ ID NO. 10 in US20050260711A1	VH	406
Her2	Pertuzumab with a signal peptide sequence	SEQ ID NO. 17 in US20060018899	VL	407
Her2	Pertuzumab with a signal peptide sequence	SEQ ID NO. 18 in US20060018899	VH	408
Her2	Periplasmic Fab-4D5	SEQ ID NO. 30 in US 7,632,924	VL	409

Her2	Periplasmic Fab-4D5	SEQ ID NO. 31 in US 7,632,924	VH	410
Her2	trastuzumab A88C	SEQ ID NO. 6 in US7521541	VH	411
Her2	trastuzumab A121C	SEQ ID NO. 7 in US7521541	VH	412
Her2	trastuzumab V110C	SEQ ID NO. 8 in US7521541	VL	413
Her2	B1D2	SEQ ID NO. 42 in US7,332,585	VH	414
Her2	B1D2	SEQ ID NO. 47 in US7,332,585	VL	415
Her2	Fab63	SEQ ID NO. 7 in US20100047230	VH	416
Her2	Fab63	SEQ ID NO. 8 in US20100047230	VL	417
Her2	Herceptin	SEQ ID NO. 3 in US20160256561	VH	418
Her2	anti-her2/neu antibody with a signal peptide	SEQ ID NO. 1 in US 9,534,057	VH	419
Her2	anti-her2/neu antibody with a signal peptide	SEQ ID NO. 2 in US 9,534,057	VL	420
anti-Her2/neu - anti-CD3	anti-Her2/neu - anti-CD3 bispecific antibody VH	SEQ ID NO. 3 in WO2014079000A1	VH	421

Chimeric antigen receptors (CARs)

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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).

[00212] 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.

[00213] 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.

[00214] 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 *invivo*.

[00215] 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*.

Extracellular targeting domain/moiety

[00216] 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.

[00217] 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.

[00218] In some embodiments, natural ligands may be used as the targeting moieties of the CARs of the present invention. Such natural ligands may be capable of binding to the antigens with affinity in the range of the scFvs and can redirect T cells specificity and effector functions to target cells expressing the complementary receptor. In some embodiments, the targeting moiety of the CAR may be neuregulin-1 (NRG1) which is a natural ligand for HER3 and HER4; VEGF which is a natural ligand of VEGFR; IL13 wildtype protein or IL13 mutein e.g. E13Y which binds to IL13Ra2; NKG2D ligand, which is a natural ligand of NKG2D receptor; CD70 which is ligand of CD27; and a proliferation-inducing ligand (APRIL) which is a natural high affinity ligand for BCMA8 and transmembrane activator and CAML interactor (TACI). Any of the ligand based BCMA CARs taught in the US Patent Publication No. US20160362467A1, the contents of which are incorporated by reference in their entirety.

[00219] In one embodiment, the targeting moiety of the CAR may recognize antigen such as, but not limited to a ganglioside, a growth factor receptor, a lectin or any other cell surface antigen. In some embodiments, any of the sequences described in Table 7 or Table 8 may be useful in the present invention.

[00220] 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

[00221] In some embodiments, the targeting moieties of the present invention may be scFv comprising the amino acid sequences in Table 8.

Table 8: scFv sequences

Target	Description and Clone name	Source	SEQ ID NO.
ALK	ALK15 scFv	SEQ ID NO. 17 in WO2015069922	422
ALK	ALK48 scFv	SEQ ID NO. 18 in WO2015069922	423
ALK	ALK53 scFv	SEQ ID NO. 19 in WO2015069922	424
ALK	ALK58 scFv	SEQ ID NO. 20 in WO2015069922	425
ALK	humanized ALK15 scFv	SEQ ID NO. 21 in WO2015069922	426
ALK	humanized ALK48 scFv	SEQ ID NO. 22 in WO2015069922	427
ALK	humanized ALK53 scFv	SEQ ID NO. 23 in WO2015069922	428
ALK	humanized ALK58 scFv	SEQ ID NO. 24 in WO2015069922	429
CD22	CD22 (m971) scFv	SEQ ID NO. 9 in WO2014065961	430
CD22	CD22 (HA22 or BL22) scFv	SEQ ID NO. 5 in WO2013059593	431
CD22	CD22 (HA22 or BL22) scFv	SEQ ID NO. 6 in WO2013059593	432
CD276	CD276 scFv	SEQ ID NO. 21 in WO2017044699	433
CD276	CD276 scFv (CD276.6)	SEQ ID NO. 10 in WO2014160627	434
CD276	CD276 scFv (CD276.1)	SEQ ID NO. 19 in WO2014160627	435
CD276	CD276 scFv (CD276.17)	SEQ ID NO. 28 in WO2014160627	436
GD2	hu3F8/huOKT3 scFv	SEQ ID No. 23 in WO2011160119	437
GD2	hu3F8/C8.2.5 scFv	SEQ ID No. 24 in WO2011160119	438
Gangliosides including GD2	DMab14-86184 scFv	SEQ ID No. 6 in WO2012071216	439
Gangliosides including GD2	GMab1 scFv	SEQ ID No. 20 in WO2012071216	440
Gangliosides including GD2	GMab2 scFV	SEQ ID No. 21 in WO2012071216	441
Gangliosides including GD2	DMab14 scFV	SEQ ID No. 22 in WO2012071216	442
GD2	GD2 scFv	SEQ ID NO. 19 in WO2016134286	443
GD2	GD2 scFv	SEQ ID NO. 20 in WO2016134287	444
GD2	GD2 scFv	SEQ ID NO. 21 in WO2016134288	445
GD2	Murine KM666 sequence	SEQ ID NO. 7 in WO2015132604	446
GD2	Humanized KM666 sequence	SEQ ID NO. 8 in WO2015132604	447
GD2	GD2 scFv	SEQ ID NO. 11 in US20160032009	448
GD2	GD2 scFv	SEQ ID NO. 12 in US20160032009	449
GD2	GD2 scFv	SEQ ID NO. 13 in US20160032009	450
GD2	GD2 scFv	SEQ ID NO. 14 in US20160032009	451
GD2	GD2 scFv	SEQ ID NO. 15 in US20160032009	452
GD2	GD2 scFv	SEQ ID NO. 16 in US20160032009	453

GD2	GD2 scFv	SEQ ID NO. 17 in US20160032009	454
GD2	GD2 scFv	SEQ ID NO. 18 in US20160032009	455
GD2	GD2 scFv	SEQ ID NO. 19 in US20160032009	456
GD2	GD2 scFv	SEQ ID NO. 20 in US20160032009	457
GD2	GD2 scFv	SEQ ID NO. 21 in US20160032009	458
GD2	GD2 scFv	SEQ ID NO. 22 in US20160032009	459
GD2	GD2 scFv	SEQ ID NO. 23 in US20160032009	460
GD2	GD2 scFv	SEQ ID NO. 24 in US20160032009	461
GD2	GD2 scFv	SEQ ID NO. 25 in US20160032009	462
GD2	Murine KM666 scFv sequence	SEQ ID NO. 7 in US20170066838	463
GD2	Humanized KM666 scFv sequence	SEQ ID NO. 8 in US20170066838	464
GD2	GD2 (clone 1A7) scFv	SEQ ID NO. 1 in US 20050287148A1	465
Her2	F5	SEQ ID NO. 1 in US 9,388,244	466
Her2	C1	SEQ ID NO. 2 in US 9,388,244	467
anti-Her2/neu - anti-CD3	anti-Her2/neu - anti-CD3 bispecific antibody scFv	SEQ ID NO. 1 in WO2014079000A1	468
Her2	F5	SEQ ID NO. 1 in US7,332,580	469
Her2	HER3.B12	SEQ ID NO. 6 in US7,332,580	470
Her2	FL/Fc/HER2Fv - Flt3 ligand extracellular region (hFLex); IgG1 Fc; rhuMAb ScFv	SEQ ID NO. 62 in US20040254108	471
Her2	Periplasmic 6×-His (SEQ ID NO. 933) C terminal scFv-4D5	SEQ ID NO. 26 in US 7,632,924	472
Her2	Periplasmic 6×-His (SEQ ID NO. 933) N terminal scFv-4D5	SEQ ID NO. 28 in US 7,632,924	473

Intracellular signaling domains

[00222] 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).

[00223] 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 if it transduces the effector function signal.

[00224] 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.

[00225] 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. NOS. 9, 175, 308; the contents of which are incorporated herein by reference in its entirety.

[00226] 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, IL-15Ra, 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.

[00227] 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.

[00228] 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.

[00229] In some embodiments, the intracellular domain of the present invention may comprise amino acid sequences of Table 9.

Table 9: Intracellular signaling and co-stimulatory

Domain	Sequence	SEQ ID NO
2B4 co-stimulatory domain	WRRKRKEKQSETSPKEFLTIYEDVKDLKTRRNHEQEQTFPGGGSTIYSMIQ SQSSAPTSQEPAYTLYSLIQPSRKSGSRKRNHSPSFNSTIYEVIGKSQPKAQ NPARLSRKELENFDVYS	474
CD27 co-stimulatory domain	HQRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACSP	475
CD272 (BTLA1) co-stimulatory domain	RRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDN DPDLCFRMQEGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNVKEAP TEYASICVRS	476

CD272 (BTLA1) co-stimulatory domain	CCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGI YDNDPDLCFRMQEGSEVYSNPCLEENKPGIVYASLNHSVIGPNSRLARNV KEAPTEYASICVRS	477
CD28 co-stimulatory	FWVLVVVGGVLACYSLLVTVAFIIFWV	478
CD28 co-stimulatory domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	479
CD28 co-stimulatory domain	FWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	480
CD28 co-stimulatory domain	RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	481
CD28 co-stimulatory domain	RSKRSRGGHSDYIVINMTPRRPGPTRKHYQPYAPPRDFAAYRS	482
CD28 co-stimulatory signaling region	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSRE FRASLHKGLDSAVEVCVVYGNYSQQLQVYSKTGFNCDGKLGNESVTFYL QNLYVNQTDIYFCKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPS KPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDFAAYRS	483
CD30 co-stimulatory domain	RRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLRSGASVTEPVAE ERGLMSQPLMETCHSVGAAYLESLPLQDASPAGGPSSPRDLPEPRVSTEHT NNKIEKIYIMKADTVIVGTVKAELPEGRGLAGPAEPELEEELEADHTPHYP EQETEPPLGSCSDVMLSVEEEGKEDPLPTAASGK	484
GITR co-stimulatory domain	HIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEEKGRLG DLWV	485
HVEM co-stimulatory domain	CVKRRKPRGDVVKVIVSVQRKRQEAEGEATVIEALQAPPDVTTVAVEETI PSFTGRSPNH	486
ICOS co-stimulatory domain	TKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL	487
ICOS co-stimulatory signaling domain	CWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL	488
LAG-3 co-stimulatory region	HLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPEPEPEPEPEPEPE QL	489
OX40 co-stimulatory domain	ALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	490
OX40 co-stimulatory domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	491
4-1BB intracellular domain	KRGRKKLLYIFKQPFMRPVQTIQEEDGCSCRFPEEEEGGCEL	492
4-1BB signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGYEL	493
4-1BB-CD3Zeta intracellular domain	TGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA PLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR	494
4-1BB-Z endodomain fusion	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR	495
CD127 intracellular domain	KRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLDCQIHRVDDIQA RDEVEGFLQDTFPQQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSL TCLAGNVSACDAPILSSSRSLDCRESGKNGPHVYQDLLLSLGTTNSTLPPPF SLQSGILTLNPVAQGQPILTSLGSNQEEAYVTMSSFYQNQ	496
CD137 intracellular domain	RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	497

CD148 intracellular domain	RKKRKDAKNNEVSFSQIKPKKSKLIRVENFEAYFKKQQADSNCGFAEEYE DLKLVGISQPKYAAELAENRGKNRYNNVLPYDISRVKLSVQTHSTDDYIN ANYMPGYHSKKDFIATQGPLPNTLKDFWRMVWEKNVYAIIMLTKCVEQ GRTKCEEYWPSKQAQDYGDITVAMTSEIVLPEWTIRDFTVKNIQTSESHPL RQFHFTSWPDHGVPDTTDLLINFRYLVRDYMKQSPPESPILVHCSAGVGR TGTFIAIDRLIYQIENENTVDVYGIVYDLRMHRPLMVQTEDQYVFLNQCV LDIVRSQKDSKVDLIYQNTTAMTIYENLAPVTTFGKTNGYIA	498
CD27 intracellular domain	QRRKYRSNKGESPVEPAEPCHYSCPREEEGSTIPIQEDYRKPEPACSP	499
CD28 intracellular domain	FAAYRS	500
CD28 signaling chain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAYRS	501
CD28 signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	502
CD28 signaling domain	SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	503
CD28 signaling domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLA CYSLLVTVAFIIFWRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDF AAYRS	504
CD28, 4-1BB, and/or CD3ζ signaling domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRG RKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR	505
CD28/CD3C	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGG VLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR	506
CD28-0XZ intracellular domain	RSKRSRLLHSDYNMTPRRPGPTRKHYQPYAPPRDFAAYRSRDQRLPPDAH KPPGGGSFRTPIQEEQADAHSTLAKIRVKFSRSADAPAYQQGQNQLYNEL NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	507
CD28-4-1BB intracellular domain	MFWVLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCEL	508
CD28-4-1BB intracellular domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE EGGCEL	509
CD28-CD3 Zeta intracellular domain	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSA DAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	510
CD28-CD3Zeta intracellular domain	KRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADA PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR	511
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITWVEGTVGTLL SDITRLDLGKRILDPRGIYRCNGTDIYKDKESTVQVHYRMCQSCVELDPAT VAGIIVTDVIATLLLALGVFCFAGHETGRLSGAADTQALLRNDQVYQPLR DRDDAQYSHLGGNWARNK	512
CD3 delta chain intracellular signaling domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITWVEGTVGTLL SDITRLDLGKRILDPRGIYRCNGTDIYKDKESTVQVHYRTADTQALLRND QVYQPLRDRDDAQYSHLGGNWARNK	513
CD3 delta chain intracellular signaling domain	DQVYQPLRDRDDAQYSHLGGN	514

CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITWVEGTVGTLL SDITRLDLGKRILDPRGIYRCNGTDIYKDKESTVQVHYRMCQSCVELDPAT VAGIIVTDVIATLLLALGVFCFAGHETGRLSGAADTQALLRNDQVYQPLR DRDDAQYSHLGGNWARNK	515
CD3 delta intracellular domain	MEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITWVEGTVGTLL SDITRLDLGKRILDPRGIYRCNGTDIYKDKESTVQVHYRTADTQALLRND QVYQPLRDRDDAQYSHLGGNWARNK	516
CD3 epsilon intracellular domain	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCP QYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYP RGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYY WSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLY SGLNQRRI	517
CD3 epsilon intracellular domain	NPDYEPIRKGQRDLYSGLNQR	518
CD3 gamma intracellular domain	MEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQEDGSVLLTCDAEA KNITWFKDGKMIGFLTEDKKKWNLGSNAKDPRGMYQCKGSQNKSKPLQ VYYRMCQNCIELNAATISGFLFAEIVSIFVLAVGVYFIAGQDGVRQSRASD KQTLLPNDQLYQPLKDREDDQYSHLQGNQLRRN	519
CD3 gamma intracellular domain	DQLYQPLKDREDDQYSHLQGN	520
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLR VKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP QRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	521
CD3 zeta intracellular domain	NQLYNELNLGRREEYDVLDKR	522
CD3 zeta domain 2 (NM_000734.3)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	523
CD3 zeta intracellular domain	DGLYQGLSTATKDTYDALHMQ	524
CD3 zeta intracellular domain	RVKFSRSAEPPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR	525
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	526
CD3 zeta intracellular domain	RSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR	527
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR	528
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEVDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	529
CD3 zeta intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLVGIVLTLLVCRLKIQVRK AAITSYEKSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAVSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR	530
CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	531
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PQRRKNPQEGLY	532

CD3 zeta intracellular domain	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR	533
CD3 zeta intracellular domain	RRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	534
CD3 zeta intracellular domain	EGLYNELQKDKMAEAYSEIGMK	535
CD3 zeta intracellular domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	536
CD3 zeta intracellular domain	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALP	537
CD3 zeta intracellular domain	DPKLCYLLDGILFIYGVILTALFLRVKFSRSADAPAYQQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	538
CD3 zeta intracellular domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLR VKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR	539
CD40 intracellular domain	RSRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	540
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKVPASLMVSLGED AHFQCPHNSSNNANVTWWRVLHGNYTWPPEFLGPGEDPNGTLIIQNVNK SHGGIYVCRVQEGNESYQQSCGTYLRVRQPPPRPFLDMGEGTKNRIITAEG IILLFCAVVPGTLLLFRKRWQNEKLGLDAGDEYEDENLYEGLNLDDCSMY EDISRGLQGTYQDVGSLNIGDVQLEKP	541
CD79A intracellular domain	MPGGPGVLQALPATIFLLFLLSAVYLGPGCQALWMHKVPASLMVSLGED AHFQCPHNSSNNANVTWWRVLHGNYTWPPEFLGPGEDPNEPPPRPFLDM GEGTKNRIITAEGIILLFCAVVPGTLLLFRKRWQNEKLGLDAGDEYEDENL YEGLNLDDCSMYEDISRGLQGTYQDVGSLNIGDVQLEKP	542
CD79A intracellular domain	ENLYEGLNLDDCSMYEDISRG	543
CD8 intracellular domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNR	544
CD8 intracellular domain	FVPVFLPAKPITTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNR	545
CD8a intracellular domain	PTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI	546
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVFVKMAPTEAECEKQFQPYFIPIN	547
CTLA4 intracellular domain	AVSLSKMLKKRSPLTTGVYMNMTPRRPECEKQFQPYAPPRDFAAYRS	548
DAP10 intracellular domain	RPRRSPAQDGKVYINMPGRG	549
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESPYQELQGQRSD VYSDLNTQRPYYK	550
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEATRKQRITETESPYQELQGQRSDV YSDLNTQRPYYK	551

DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDLVLTVLIALAVY FLGRLVPRGRGAAEAATRKQRITETESPYQELQGQRSDVYSDLNTQRPYY K	552
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDLVLTVLIALAVY FLGRLVPRGRGAAEATRKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	553
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESPYQELQGQRSD VYSDLNTQRPYYK	554
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSGLRPVQAQAQSDCSCSTVSPGVLAGIVMGD LVLTVLIALAVYFLGRLVPRGRGAAEAATRKQRITETESPYQELQGQRSDV YSDLNTQRPYYK	555
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDLVLTVLIALAVY FLGRLVPRGRGAAEAATRKQRITETESPYQELQGQRSDVYSDLNTQRPYY K	556
DAP12 intracellular domain	MGGLEPCSRLLLLPLLLAVSDCSCSTVSPGVLAGIVMGDLVLTVLIALAVY FLGRLVPRGRGAAEATRKQRITETESPYQELQGQRSDVYSDLNTQRPYYK	557
DAP12 intracellular domain	ESPYQELQGQRSDVYSDLNTQ	558
GITR intracellular domain	RSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEEKGRLGDLWV	559
ICOS intracellular domain	TKKKYSSSVHDPNGEFMFMRAVNTAKKSRLTDVTL	560
IL- 15Ra intracellular domain	KSRQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHHL	561
OX40-CD3 Zeta intracellular domain	RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKIRVKFSRSADAPAYQ QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR	562
ZAP70 intracellular domain	MPDPAAHLPFFYGSISRAEAEEHLKLAGMADGLFLLRQCLRSLGGYVLSL VHDVRFHHFPIERQLNGTYAIAGGKAHCGPAELCEFYSRDPDGLPCNLRK PCNRPSGLEPQPGVFDCLRDAMVRDYVRQTWKLEGEALEQAIISQAPQVE KLIATTAHERMPWYHSSLTREEAERKLYSGAQTDGKFLLRPRKEQGTYAL SLIYGKTVYHYLISQDKAGKYCIPEGTKFDTLWQLVEYLKLKADGLIYCL KEACPNSSASNASGAAAPTLPAHPSTLTHPQRRIDTLNSDGYTPEPARITSP DKPRPMPMDTSVYESPYSDPEELKDKKLFLKRDNLLIADIELGCGNFGSVR QGVYRMRKKQIDVAIKVLKQGTEKADTEEMMREAQIMHQLDNPYIVRLI GVCQAEALMLVMEMAGGGPLHKFLVGKREEIPVSNVAELLHQVSMGMK YLEEKNFVHRDLAARNVLLVNRHYAKISDFGLSKALGADDSYYTARSAG KWPLKWYAPECINFRKFSSRSDVWSYGVTMWEALSYGQKPYKKMKGPE VMAFIEQGKRMECPPECPPELYALMSDCWIYKWEDRPDFLTVEQRMRAC YYSLASKVEGPPGSTQKAEAACA	563
CD28 intracellular domain	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSRE FRASLHKGLDSAVEVCVVYGNYSQQLQVYSKTGFNCDGKLGNESVTFYL QNLYVNQTDIYFCKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPS KPFWVLVVVGGVLACYSLLVTVAFIIFWVR	564
4-1BB intracellular domain	MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDNNRNQICSPCPPN SFSSAGGQRTCDICRQCKGVFRTRKECSSTSNAECDCTPGFHCLGAGCSM CEQDCKQGQELTKKGCKDCCFGTFNDQKRGICRPWTNCSLDGKSVLVNG TKERDVVCGPSPADLSPGASSVTPPAPAREPGHSPQIISFFLALTSTALLFLL FFLTLRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDG	565
Fc epsilon Receptor I gamma chain intracellular domain	MIPAVVLLLLLLVEQAAALGEPQLCYILDAILFLYGIVLTLLYCRLKIQVRK AAITSYEKSDGVYTGLSTRNQETYETLKHEKPPQ	566
Fc epsilon Receptor I gamma	DGVYTGLSTRNQETYETLKHE	567

chain intracellular domain		
Fc epsilon Receptor I gamma chain intracellular domain	DPKLCYILDAILFLYGIVLTLLYCRLKIQVRKAAITSYEKSDGVYTGLSTRN QETYETLKHEKPPQ	568
CD28 intracellular domain	SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	569
CD28 signaling domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVR	570
CD8 signaling domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNR	571
intracellular T cell signaling domain comprising CD28 and CD3 zeta	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRD FAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR	572
Intracellular T cell signaling domain comprising CD28, CD137, and CD3 zeta	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRR PGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	573

Transmembrane domains

[00230] 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.

[00231] 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.

[00232] 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 IgG_4 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 NOS. WO2014/100385; and a PD-1 transmembrane domain comprising the amino acid sequences of SEQ ID NOs. 6-8 of International Patent Publication NOS. WO2014100385; the contents of each of which are incorporated herein by reference in their entirety.

[00233] 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 10 provides various transmembrane regions that can be used in the CARs described herein.

Table 10: Transmembrane domains

Transmembrane domain	Sequence	SEQ ID NO
CD8 Transmembrane domain	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDI	574
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVVKRGR	575
4-1BB Transmembrane domain	IISFFLALTSTALLFLLFFLTLRFSVV	576
CD134 (OX40) Transmembrane domain	VAAILGLGLVLGLLGPLAILLALYLL	577
CD148 Transmembrane and intracellular domain	AVFGCIFGALVIVTVGGFIFWRKKRKDAKNNEVS FSQIKPKKSKLIRVENFEAYFKKQQADSNCGFAEE YEDLKLVGISQPKYAAELAENRGKNRYNNVLPY DISRVKLSVQTHSTDDYINANYMPGYHSKKDFIA TQGPLPNTLKDFWRMVWEKNVYAIIMLTKCVEQ GRTKCEEYWPSKQAQDYGDITVAMTSEIVLPEVV TIRDFTVKNIQTSESHPLRQFHFTSWPDHGVPDTT	578

	DLLINFRYLVRDYMKQSPPESPILVHCSAGVGRTG TFIAIDRLIYQIENENTVDVYGIVYDLRMHRPLMV QTEDQYVFLNQCVLDIVRSQKDSKVDLIYQNTTA MTIYENLAPVTTFGKTNGYIA	
CD148 Transmembrane domain	AVFGCIFGALVIVTVGGFIFW	579
CD2 Transmembrane domain	KEITNALETWGALGQDINLDIPSFQMSDDIDDIKW EKTSDKKKIAQFRKEKETFKEKDTYKLFKNGTLK IKHLKTDDQDIYKVSIYDTKGKNVLEKIFDLKIQE RVSKPKISWTCINTTLTCEVMNGTDPELNLYQDG KHLKLSQRVITHKWTTSLSAKFKCTAGNKVSKES SVEPVSCPEKGLD	580
CD28 Transmembrane and intracellular domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPG PSKPFWVLVVVGGVLACYSLLVTVAHIFWVRSK RSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFA AYRS	581
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWV	582
CD28 Transmembrane domain	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGP SKPFWVLVVVGGVLACYSLLVTVAFIIFWV	583
CD28 Transmembrane domain	IFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRR	584
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPTRKHYQP YAPPRDFAAYRS	585
CD28 Transmembrane domain	MFWVLVVVGGVLACYSLLVTVAFIIFWV	586
CD28 Transmembrane domain	FWVLVVVGGVLACYSLLVTVAFHFWV	587
CD28 Transmembrane domain	MFWVLVVVGGVLACYSGGVTVAFIIFWV	588
CD28 Transmembrane domain	WVLVVVGGVLACYSLLVTVAFIIFWV	589
CD28 Transmembrane domain	PFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAY RS	590
CD28 Transmembrane domain and CD28 and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR SRVKFSRSADAPAYQQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR	591
CD28 Transmembrane domain and CD28, OX40, and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR SRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLA KIRVKFSRSADAPAYQQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR	592

CD28 Transmembrane domain and CD3 Zeta intracellular domain	FWVLVVVGGVLACYSLLVTVAFIIFWVRRVKFSR SADAPAYQQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	593
CD28 transmembrane-CD3 zeta signaling domain ("28z")	AAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPL FPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWV RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPR DFAAYRSRVKFSRSADAPAYQQGQNQLYNELNL GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR	594
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFLRV	595
CD3 zeta Transmembrane domain	MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYL LDGILFIYGVILTALFL	596
CD3 zeta Transmembrane domain	LCYLLDGILFIYGVILTALFL	597
CD4 Transmembrane domain	ALIVLGGVAGLLLFIGLGIFFCVRC	598
CD4 Transmembrane domain	MALIVLGGVAGLLLFIGLGIFF	599
CD45 Transmembrane and intracellular domain	ALIAFLAFLIIVTSIALLVVLYKIYDLHKKRSCNLD EQQELVERDDEKQLMNVEPIHADILLETYKRKIA DEGRLFLAEFQSIPRVFSKFPIKEARKPFNQNKNR YVDILPYDYNRVELSEINGDAGSNYINASYIDGFK EPRKYIAAQGPRDETVDDFWRMIWEQKATVIVM VTRCEEGNRNKCAEYWPSMEEGTRAFGDVVVKI NQHKRCPDYIIQKLNIVNKKEKATGREVTHIQFTS WPDHGVPEDPHLLLKLRRRVNAFSNFFSGPIWHC SAGVGRTGTYIGIDAMLEGLEAENKVDVYGYVV KLRRQRCLMVQVEAQYILIHQALVEYNQFGETEV NLSELHPYLHNMKKRDPPSEPSPLEAEFQRLPSYR SWRTQHIGNQEENKSKNRNSNVIPYDYNRVPLKH ELEMSKESEHDSDESSDDDSDSEEPSKYINASFIM SYWKPEVMIAAQGPLKETIGDFWQMIFQRKVKVI VMLTELKHGDQEICAQYWGEGKQTYGDIEVDLK DTDKSSTYTLRVFELRHSKRKDSRTVYQYQYTN WSVEQLPAEPKELISMIQVVKQKLPQKNSSEGNKH HKSTPLLIHCRDGSQQTGIFCALLNLLESAETEEW DIFQVVKALRKARPGMVSTFEQYQFLYDVIASTYP AQNGQVKKNNHQEDKIEFDNEVDKVKQDANCV NPLGAPEKLPEAKEQAEGSEPTSGTEGPEHSVNGP ASPALNQGS	600
CD62L Transmembrane domain	PLFIPVAVMVTAFSGLAFIIWLA	601
CD7 Transmembrane domain	ALPAALAVISFLLGLGLGVACVLA	602
CD8 Transmembrane domain	MALPVTALLLPLALLLHAARP	603
CD8 Transmembrane domain and CD28 signaling domain	AAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLR PEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCG VLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKK LLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE	604

	LRVKFSRSADAPAYQQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR	
CD8 transmembrane domain-CD137 (4-1BB) signaling domain and CD3 zeta signaling domain ("BBz")	AAATTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYKQGQNQLYNEL NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR	605
CD8a Transmembrane domain	FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL LSLVITLYCNHRN	606
CD8a Transmembrane domain	IWAPLAGTCGVLLLSLVITLYC	607
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	608
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYCR	609
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLVCR	610
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVIT	611
CD8a Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLY	612
CD8b Transmembrane domain	LGLLVAGVLVLLVSLGVAIHLCC	613
EpoR Transmembrane domain	APVGLVARLADESGHVVLRWLPPPETPMTSHIRY EVDVSAGNGAGSVQRVEILEGRTECVLSNLRGRT RYTFAVRARMAEPSFGGFWSAWSEPVSLLTPSD	614
FcER1 a- Transmembrane domain	MAPAMESPTLLCVALLFFAPDGVLAVPQKPKVSL NPPWNRIFKGENVTLTCNGNNFFEVSSTKWFHNG SLSEETNSSLNIVNAKFEDSGEYKCQHQQVNESEP VYLEVFSDWLLLQASAEVVMEGQPLFLRCHGWR NWDVYKVIYYKDGEALKYWYENHNISITNATVE DSGTYYCTGKVWQLDYESEPLNITVIKAPREKYW LQFFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRT RKGFRLLNPHPKPNPKNN	615
FceRIa Transmembrane domain	DIFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRK GFRLLNPHPKPNPKNNR	616
GITR Transmembrane domain	PLGWLTVVLLAVAACVLLLTSAQLGLHIWQL	617
Her2 Transmembrane domain	SIISAVVGILLVVVLGVVFGILI	618
Her2 Transmembrane domain	CHPECQPQNGSVTCFGPEADQCVACAHYKDPPFC VARCPSGVKPDLSYMPIWKFPDEEGACQPCPINC THSCVDLDDKGCPAEQRASPLTSIISAVVGILLVV VLGVVFGILI	619
ICOS Transmembrane domain	FWLPIGCAAFVVVCILGCILI	620

IgG1Transmembrane domain	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTL MIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGKKD	621
OX40 Transmembrane domain	VAAILGLGLVLGLLGPLAILL	622
Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	623
Transmembrane domain	IYIWAPLAGTCGVLLLSLVITLYC	624
CD28 transmembrane and signaling domains	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGP SKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFA AYRS	625
CD28 Transmembrane domain	VMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPS KPFWVLVVVGGVLACYSLLVTVAFIIFWVR	626
CD8 Transmembrane domain	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC	627

[00234] Hinge region sequences useful in the present invention are provided in Table 11.

Table 11: Hinge regions

Hinge Domain	Sequence	SEQ ID NO
Hinge	DKTHT	628
Hinge	CPPC	629
Hinge	CPEPKSCDTPPPCPR	630
Hinge	ELKTPLGDTTHT	631
Hinge	KSCDKTHTCP	632
Hinge	KCCVDCP	633
Hinge	KYGPPCP	634
C233P Hinge	VEPKSPDKTHTCPPCP	635
C233S Hinge	LDPKSSDKTHTCPPCP	636
CD28 Hinge	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP	637
CD8a Hinge	GGAVHTRGLDFA	638
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	639
CD8a Hinge	AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	640
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDEPKSP DKTHTCPPCPAPPVAGPSVFLFPPKPKDT	641
CD8a Hinge	PAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI Y	642
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA PLAGTCGVLLLSLVITLYC	643
CD8a Hinge	TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	644
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY	645
Delta5 Hinge	LDKTHTCPPCP	646

EpoR Hinge	APVGLVARLADESGHVVLRWLPPPETPMTSHIRYEVDVSAGNGAGSV QRVEILEGRTECVLSNLRGRTRYTFAVRARMAEPSFGGFWSAWSEPVS LLTPSD	647
FCRIIα Hinge	GLAVSTISSFFPPGYQ	648
Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	649
Hinge	YVTVSSQDPAEPKSPDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGKKDPK	650
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA	651
Hinge	LEPKSCDKTHTCPPCP	652
Hinge	KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD	653
Hinge	ELKTPLGDTHTCPRCP	654
Hinge	EPKSCDTPPPCPRCP	655
Hinge	ESKYGPPCPSCP	656
Hinge	ERKCCVECPPCP	657
Hinge (CH2-CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	658
Hinge (CH3)	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	659
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	660
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEAA SWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAW SVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	661
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMVVLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	662
IgD Hinge	ESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKE EQEERETKTP	663
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	664

IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	665
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAW SVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	666
IgD Hinge	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKE KEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVV GSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEA ASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWA WSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	667
IgG1 (CH2CH3) Hinge domain	AEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	668
IgG1 Hinge	AEPKSPDKTHTCPPCPKDPK	669
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEVKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLV SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKD	670
IgG1 Hinge	SVFLFPPKPKDTL	671
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	672
IgG1 Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKDPK	673
IgG1 Hinge	VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	674
IgG1 Hinge (CH2CH3 domain)	DPAEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKK	675
IgG3 Hinge	ELKTPLGDTTHTCPRCP	676
IgG3 Hinge	ELKTPLGDTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKS CDTPPPCPRCP	677
IgG4 (CH2 and CH3)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	678

IgG4 (CH2 and CH3)	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	679
IgG4 Hinge	SPNMVPHAHHAQ	680
IgG4 Hinge	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLGK	681
IgG4 Hinge	ESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	682
IgG4 Hinge	ESKYGPPCPSCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHQAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFVPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	683
IgG4 Hinge	ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHQAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFVPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	684
IgG4 Hinge	GAATCTAAGTACGGACCGCCCTGCCCCCCTTGCCCT	685
IgG4 Hinge	ESKYGPPCPPCP	686
IgG4 Hinge	YGPPCPPCP	687
IgG4 Hinge	KYGPPCPPCP	688
IgG4 Hinge	EVVKYGPPCPPCP	689
IgG4 Hinge	ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDLSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	690
IgG4 Hinge and Linker	ESKYGPPCPPCPGGGSSGGGSG	691
IgGl Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTIPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	692
IgGl Hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTIPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	693
CH2CH3 spacer domain	EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKKDPK	694

[00235] 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.

[00236] In some embodiments, the CH2CH3 may be preferentially excluded from the chimeric antigen structure to elicit a higher TNFa response as disclosed in WO2016149578 (the contents of which are herein incorporated by reference). In some constructs a CH2CH3 structural domain is included. This domain extends the scFV away from the plasma membrane extracellular surface, and allows for the efficient detection of transduced T cells with anti-IgG Fc-specific antibody. CAR constructs which include CH2CH3 domain are disclosed in WO2015069922A3 (the contents of which are incorporated herein by reference in its entirety).

[00237] 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.

[00238] In some embodiments, the CAR sequences may be selected from Table 12.

Table 12: CAR sequences

Description	Source	Target	SEQ ID NO.
ALK CAR	SEQ ID NO. 37 in WO2015069922	ALK	695
ALK CAR	SEQ ID NO. 39 in WO2015069922	ALK	696
ALK CAR	SEQ ID NO. 41 in WO2015069922	ALK	697
ALK CAR	SEQ ID NO. 43 in WO2015069922	ALK	698
ALK CAR	SEQ ID NO. 44 in WO2015069922	ALK	699
ALK CAR	SEQ ID NO. 45 in WO2015069922	ALK	700
ALK CAR	SEQ ID NO. 46 in WO2015069922	ALK	701
ALK CAR	SEQ ID NO. 47 in WO2015069922	ALK	702
ALK CAR	SEQ ID NO. 48 in WO2015069922	ALK	703
ALK CAR	SEQ ID NO. 49 in WO2015069922	ALK	704
ALK CAR	SEQ ID NO. 50 in WO2015069922	ALK	705
ALK CAR	SEQ ID NO. 51 in WO2015069922	ALK	706
ALK CAR	SEQ ID NO. 52 in WO2015069922	ALK	707
ALK CAR	SEQ ID NO. 53 in WO2015069922	ALK	708
ALK CAR	SEQ ID NO. 54 in WO2015069922	ALK	709
ALK CAR	SEQ ID NO. 55 in WO2015069922	ALK	710
ALK CAR	SEQ ID NO. 56 in WO2015069922	ALK	711

ALK CAR	SEQ ID NO. 57 in WO2015069922	ALK	712
ALK CAR	SEQ ID NO. 58 in WO2015069922	ALK	713
ALK CAR	SEQ ID NO. 59 in WO2015069922	ALK	714
ALK CAR	SEQ ID NO. 60 in WO2015069922	ALK	715
ALK CAR	SEQ ID NO. 61 in WO2015069922	ALK	716
ALK CAR	SEQ ID NO. 62 in WO2015069922	ALK	717
ALK CAR	SEQ ID NO. 63 in WO2015069922	ALK	718
ALK CAR	SEQ ID NO. 64 in WO2015069922	ALK	719
ALK CAR	SEQ ID NO. 65 in WO2015069922	ALK	720
ALK CAR	SEQ ID NO. 66 in WO2015069922	ALK	721
ALK CAR	SEQ ID NO. 67 in WO2015069922	ALK	722
ALK CAR	SEQ ID NO. 68 in WO2015069922	ALK	723
ALK CAR	SEQ ID NO. 69 in WO2015069922	ALK	724
ALK CAR	SEQ ID NO. 70 in WO2015069922	ALK	725
ALK CAR	SEQ ID NO. 71 in WO2015069922	ALK	726
ALK CAR	SEQ ID NO. 72 in WO2015069922	ALK	727
ALK CAR	SEQ ID NO. 73 in WO2015069922	ALK	728
ALK CAR	SEQ ID NO. 74 in WO2015069922	ALK	729
ALK CAR	SEQ ID NO. 75 in WO2015069922	ALK	730
ALK CAR	SEQ ID NO. 76 in WO2015069922	ALK	731
ALK CAR	SEQ ID NO. 77 in WO2015069922	ALK	732
ALK CAR	SEQ ID NO. 78 in WO2015069922	ALK	733
ALK CAR	SEQ ID NO. 79 in WO2015069922	ALK	734
ALK CAR	SEQ ID NO. 80 in WO2015069922	ALK	735
ALK CAR	SEQ ID NO. 81 in WO2015069922	ALK	736
ALK CAR	SEQ ID NO. 82 in WO2015069922	ALK	737
ALK CAR	SEQ ID NO. 83 in WO2015069922	ALK	738
ALK CAR	SEQ ID NO. 84 in WO2015069922	ALK	739
ALK CAR	SEQ ID NO. 85 in WO2015069922	ALK	740
ALK CAR	SEQ ID NO. 86 in WO2015069922	ALK	741
ALK CAR	SEQ ID NO. 87 in WO2015069922	ALK	742
ALK CAR	SEQ ID NO. 88 in WO2015069922	ALK	743
ALK CAR	SEQ ID NO. 89 in WO2015069922	ALK	744
ALK CAR	SEQ ID NO. 90 in WO2015069922	ALK	745
CD22 (m971) third generation CAR	SEQ ID NO. 22 in WO2014065961	CD22	746
CD22 (m971) third generation CAR	SEQ ID NO. 23 in WO2014065961	CD22	747
CD22 (m971) third generation CAR	SEQ ID NO. 24 in WO2014065961	CD22	748
CD22 (CARsHA22 28z) CAR	SEQ ID NO. 15 in WO2013059593	CD22	749
CD22 (HA22 28BBz) CAR	SEQ ID NO. 16 in WO2013059593	CD22	750
CD22 (HASH22 28z) CAR	SEQ ID NO. 17 in WO2013059593	CD22	751
CD22 (HASH22 28BBz) CAR	SEQ ID NO. 18 in WO2013059593	CD22	752
CD22 (BL22 28z) CAR	SEQ ID NO. 19 in WO2013059593	CD22	753
CD22 (BL22 28BBz) CAR	SEQ ID NO. 20 in WO2013059593	CD22	754
CD22 (HA22SH-CAR-second generation, version 2) CAR	SEQ ID NO. 32 in WO2013059593	CD22	755

CD276 CAR (CD276.6 second generation)	SEQ ID NO. 39 in WO2014160627	CD276	756
CD276 CAR (CD276.1 second generation, version 1)	SEQ ID NO. 42 in WO2014160627	CD276	757
CD276 CAR (CD276.17 second generation, version 1)	SEQ ID NO. 45 in WO2014160627	CD276	758
CD276 CAR (CD276.6 CAR second generation, version 1)	SEQ ID NO. 122 in WO2014160627	CD276	759
CD276 CAR (CD276.6 CAR second generation, version 2)	SEQ ID NO. 123 in WO2014160627	CD276	760
CD276 CAR (CD276.6 CAR third generation)	SEQ ID NO. 124 in WO2014160627	CD276	761
CD276 CAR (CD276.1 CAR second generation, version 1)	SEQ ID NO. 125 in WO2014160627	CD276	762
CD276 CAR (CD276.1 CAR second generation, version 2)	SEQ ID NO. 126 in WO2014160627	CD276	763
CD276 CAR (CD276.1 CAR third generation)	SEQ ID NO. 127 in WO2014160627	CD276	764
CD276 CAR (CD276.17 CAR second generation, version 1)	SEQ ID NO. 128 in WO2014160627	CD276	765
CD276 CAR (CD276.17 CAR second generation, version 2)	SEQ ID NO. 129 in WO2014160627	CD276	766
CD276 CAR (CD276.17 CAR third generation)	SEQ ID NO. 130 in WO2014160627	CD276	767
CD 276 CAR	SEQ ID NO. 20 in WO2017044699	CD276	768
CD276.MG.BB.Z CAR	SEQ ID NO. 12 in WO2017044699	CD276	769

[00239] In one embodiment of the present invention, the payload of the invention is a CD33 specific CAR. The CD33 heavy and light chain may be combined with any of the signal peptides, transmembrane domains, costimulatory domains, intracellular domains and destabilizing domains described herein.

[00240] In one embodiment of the present invention, the payload of the invention is a GD2 specific CAR. The GD2 heavy and light chain may be combined with any of the signal peptides, transmembrane domains, costimulatory domains, intracellular domains and destabilizing domains described herein.

[00241] In one embodiment of the present invention, the payload of the invention is a Her2 specific CAR. The Her2 heavy and light chain may be combined with any of the signal peptides, transmembrane domains, costimulatory domains, intracellular domains and destabilizing domains described herein. Exemplary BCMA CAR sequences and its components are described in Table 13A. The amino acid sequences in Table 13A may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence

Table 13A: DD-Her2 construct sequences

Description	Amino Acid Sequence	Amino Acid SEQ ID NO	Nucleic Acid SEQ ID NO/ Sequence

GMCSF Leader	LLLVTSLLLCELPHPAFLLIP	778	922
Linker	ASFE	920	921
Linker	GS	-	GGTTCC, GGATCC
Linker	TS	-	ACTAGT
Linker	HM	-	ATGCAC
4-1BB Intracellular Domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CEL	773	919
4D5 scFV	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ KPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQ PEDFATYYCQQHYTTPPTFGQGTKVEIKGSTSGSGKPGS GEGSGEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYI HWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMD VWGQGTLVTVSS	923	924
CD8a Hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACD	925	926
Transmembrane Domain	IYIWAPLAGTCGVLLLSLVITLYC	927	928
CD3 Zeta signaling Domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP R	772	918
hDHFR (Amino acid 2-187 of WT; Y122I)	VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND	861	903-907
OT-Her2-004 (Met – GMCSF Leader - 4D5 scFv – Linker (ASFE) – CD8a hinge – Linker (GS) – Transmembrane Domain – Linker (TS) – 4-1BB intracellular signaling domain – Linker (HM) - CD3 zeta – Linker (GS) - hDHFR (Amino acid 2-187 of WT; Y122I) – stop)	MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDR VTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPP TFGQGTKVEIKGSTSGSGKPGSGEGSGEVQLVESGGGLV QPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAE DTAVYYCSRWGGDGFYAMDVWGQGTLVTVSSASFETT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDGSIYIWAPLAGTCGVLLLSLVITLYCTSKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELHMRVK FSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRGS VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRMT TTSSVEGKQNLVIMGKKTWFSIPEKNRPLKGRINLVLSR ELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIV GGSSVIKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLEK YKLLPEYPGVLSDVQEEKGIKYKFEVYEKND*	906	907

[00242] In one embodiment, the CAR of the present invention is a BCMA (B-cell maturation antigen) CAR, also referred to as the CD269. The BCMA heavy and light chains may be combined with any of the signal peptides, transmembrane domains, costimulatory domains, intracellular domains and destabilizing domains described herein. Exemplary BCMA CAR sequences and its components are described in Table 13B. The amino acid sequences in Table

13B may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence.

Table 13B: BCMA CAR

Description	Amino Acid Sequence	Amino Acid SEQ ID NO.	Nucleic Acid SEQ ID NO.
BCMA scFv (C11D5.3)	DIVLTQSPASLAMSLGKRATISCRASESVSVIGAHL IHWYQQKPGQPPKLLIYLASNLETGVPARFSGSGS GTDFTLTIDPVEEDDVAIYSCLQSRIFPRTFGGGTK LEIKGSTSGSGKPGSGEGSTKGQIQLVQSGPELKK PGETVKISCKASGYTFTDYSINWVKRAPGKGLKW MGWINTETREPAYAYDFRGRFAFSLETSASTAYL QINNLKYEDTATYFCALDYSYAMDYWGQGTSVT VSS	770	916
CD8α hinge--TM	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC	771	917
CD3 zeta signaling domain	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	772	918
4-1BB intracellular signaling domain	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCEL	773	919
CD8α leader	MALPVTALLLPLALLLHAARP	131	132-136, 915
ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I)	ISLIAALAVDYVIGMENAMPWNLPADLAWFKRN TLNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDD RVTWVKSVDEAIAACGDVPEIMVIGGGRVIEQFLP KAQKLYLTHIDAEVEGDTHFPDYEPDDWESVFSE FHDADAQNSHSYCFEILERR	9	61, 869-874
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDG KKVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQM SVGQGAKLTISPDYAYGATGHPGIIPPHATLVFDV ELLELE	12	88, 883-889
OT-BCMA-001 (CD8a leader- BCMA scFv - CD8a hinge—Tm – 4-1BB intracellular domain – CD3 zeta - stop)	MALPVTALLLPLALLLHAARPDIVLTQSPASLAMS LGKRATISCRASESVSVIGAHLIHWYQQKPGQPPK LLIYLASNLETGVPARFSGSGSGTDFTLTIDPVEED DVAIYSCLQSRIFPRTFGGGTKLEIKGSTSGSGKPG SGEGSTKGQIQLVQSGPELKKPGETVKISCKASGY TFTDYSINWVKRAPGKGLKWMGWINTETREPAY AYDFRGRFAFSLETSASTAYLQINNLKYEDTATYF CALDYSYAMDYWGQGTSVTVSSTTTPAPRPPTPA PTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR*	775	833
OT-BCMA-002 (CD8a leader - BCMA scFv - CD8a hinge—Tm – 4-1BB intracellular domain - CD3 zeta - Linker (SG) - FKBP (E31G, F36V, R71G, K105E) - stop)	MALPVTALLLPLALLLHAARPDIVLTQSPASLAMS LGKRATISCRASESVSVIGAHLIHWYQQKPGQPPK LLIYLASNLETGVPARFSGSGSGTDFTLTIDPVEED DVAIYSCLQSRIFPRTFGGGTKLEIKGSTSGSGKPG SGEGSTKGQIQLVQSGPELKKPGETVKISCKASGY TFTDYSINWVKRAPGKGLKWMGWINTETREPAY AYDFRGRFAFSLETSASTAYLQINNLKYEDTATYF CALDYSYAMDYWGQGTSVTVSSTTTPAPRPPTPA PTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI	776	834

	WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRSGGVQVETISPGDGRTFPKRGQTCVVHY TGMLGDGKKVDSSRDRNKPFKFMLGKQEVIRGW EEGVAQMSVGQGAKLTISPDYAYGATGHPGIIPPH ATLVFDVELLELE*		
OT-BCMA-003 (CD8a leader - BCMA scFv - CD8a hinge---Tm -- 4-1BB intracellular domain - CD3 zeta - Linker (SG) - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - stop)	MALPVTALLLPLALLLHAARPDIVLTQSPASLAMS LGKRATISCRASESVSVIGAHLIHWYQQKPGQPPK LLIYLASNLETGVPARFSGSGSGTDFTLTIDPVEED DVAIYSCLQSRIFPRTFGGGTKLEIKGSTSGSGKPG SGEGSTKGQIQLVQSGPELKKPGETVKISCKASGY TFTDYSINWVKRAPGKGLKWMGWINTETREPAY AYDFRGRFAFSLETSASTAYLQINNLKYEDTATYF CALDYSYAMDYWGQGTSVTVSSTTTPAPRPPTPA PTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPRSGISLIAALAVDYVIGMENAMPWNLPAD LAWFKRNTLNKPVIMGRHTWESIGRPLPGRKNIIL SSQPGTDDRVTWVKSVDEAIAACGDVPEIMVIGG GRVIEQFLPKAQKLYLTHIDAEVEGDTHFPDYEPD DWESVFSEFHDADAQNSHSYCFEILERR*	777	835

Tandem CAR (TanCAR)

[00243] 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

[00244] 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.

[00245] 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.

[00246] 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

[00247] 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

[00248] 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

[00249] 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).

4. Additional effector module features

[00250] 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

[00251] 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.

[00252] 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).

[00253] 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.

[00254] 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 (amino acid of SEQ ID NO. 49, encoded by the nucleic acid sequence of SEQ ID NO. 55-56 and/or 117-118), p40 signal sequence (amino acid sequence of SEQ ID NO. 119, encoded by the nucleic acid sequence of SEQ ID NO. 120-128), or a GMCSF leader sequence (SEQ ID NO. 778 (encoded by SEQ ID NO. 922), 779, 780).

[00255] 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 (amino acid SEQ ID NO. 129 and nucleotide sequence of SEQ ID NO. 130), CD8a signal sequence (also referred to as CD8a leader) (amino acid SEQ ID NO. 131 and nucleotide sequence of SEQ ID NO. 132-136, and/or 915) or an IL15Ra signal sequence (amino acid SEQ ID NO. 781, encoded by SEQ ID NO. 782).

[00256] 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 NOS. 20070141666; and International patent application publication NOS. WO1993018181; the contents of each of which are incorporated herein by reference in their entirety.

[00257] 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. NOS. 8,093,016 to Cervin and Kim), bacterial lipoprotein signal sequences (e.g., PCT application publication NOS. WO199109952 to Lau and Rioux), *E.coli* enterotoxin II signal peptides (e.g., U.S. Pat. NOS. 6,605,697 to Kwon et al.), *E.coli* secretion signal sequence (e.g., U.S. patent publication NOS. US2016090404 to Malley et al.), a lipase signal sequence from a methylotrophic yeast (e.g., U.S. Pat. NOS. 8,975,041), and signal peptides for DNases derived from *Coryneform bacteria* (e.g., U.S. Pat. NOS. 4,965,197); the contents of each of which are incorporated herein by reference in their entirety.

[00258] 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. NOS. 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. NOS. 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).

[00259] In some embodiments, signal sequences 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 which are incorporated herein by reference in their entirety.

Cleavage sites

[00260] 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.

[00261] 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.

[00262] In one embodiment, the cleavage site is a furin cleavage site comprising the amino acid sequence SARNRQKRS (SEQ ID NO. 137), encoded by nucleotide sequence of SEQ ID NO. 138; or a revised furin cleavage site comprising the amino acid sequence ARNRQKRS (SEQ ID NO. 139), encoded by nucleotide sequence of SEQ ID NO. 140; modified furin site comprising the amino acid sequence ESRRVRRNKRSK (SEQ ID NO. 141), encoded by nucleotide sequence of SEQ ID NO. 142-144; or a SGESRRVRRNKRSK (SEQ ID NO. 785), encoded by the nucleotide sequence of SEQ ID NO. 784. In some instances, the cleavage site is a P2A cleavage site (ATNFSLLKQAGDVEENPGP (SEQ ID NO. 783), encoded by SEQ ID NO. 786, or GATNFSLLKQAGDVEENPGP (SEQ ID NO.. 864), encoded by SEQ ID NO. 865), wherein NPGP (SEQ ID NO. 866) is the P2A site.

[00263] 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 which are incorporated herein by reference in their entirety.

Protein tags

[00264] 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.

[00265] 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 NOS. WO2013091661; the contents of each of which are incorporated herein by reference in their entirety.

[00266] 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.

[00267] In one embodiment, the protein tag is an HA tag. A non-limiting example of an HA tag is YPYDVPDYA (SEQ ID NO. 852, encoded by SEQ ID NO. 853, 867, and/or 868).

[00268] 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 which are incorporated herein by reference in their entirety.

Targeting peptides

[00269] 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.

[00270] 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.

[00271] 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.

[00272] 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.

[00273] 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, the contents of which are incorporated herein by reference in their entirety.

Linkers

[00274] 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.

[00275] 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).

[00276] 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. 145; encoded by the nucleotide sequence SEQ ID NO. 146), GGSGG (SEQ ID NO. 147; encoded by any of the nucleotide sequences SEQ ID NO. 148-152), GGSGGG (SEQ ID NO. 153; encoded by any of the nucleotide sequences SEQ ID NO. 154-155) , SGGGS (SEQ ID NO. 68; encoded by the nucleotide sequence SEQ ID NO. 85, 69, 86), GGSGGGSGG (SEQ ID NO. 156; encoded by the nucleotide sequence SEQ ID NO. 157), GGGGG (SEQ ID NO. 158), GGGGS (SEQ ID NO. 159) or (GGGGS)n (n=1 (SEQ ID NO. 159), 2 (SEQ ID NO. 160), 3 (SEQ ID NO. 161, encoded by 174, 175, 171, 219, 774, 837), 4 (SEQ ID NO. 162), 5 (SEQ ID NO. 163), or 6 (SEQ ID NO. 164)), SSSSG (SEQ ID NO. 165) or (SSSSG)n (n=1 (SEQ ID NO. 165), 2 (SEQ ID NO. 166), 3 (SEQ ID NO. 167), 4 (SEQ ID NO. 168), 5 (SEQ ID NO. 169), or 6 (SEQ ID NO. 170)), SGGGSGGGGSGGGGSGGGGSGGGSLQ (SEQ ID NO. 171; encoded by the nucleotide sequence SEQ ID NO. 172, 838-843), EFSTEF (SEQ ID NO. 50; encoded by any of the nucleotide sequences SEQ ID NO. 57, 173), GKSSGSGSESKS (SEQ ID NO. 176), GGSTSGSGKSSEGKG (SEQ ID NO. 177), GSTSGSGKSSSEGSGSTKG (SEQ ID NO. 178), GSTSGSGKPGSGEGSTKG (SEQ ID NO. 179), VDYPYDVPDYALD (SEQ ID NO. 67; encoded by nucleotide sequence SEQ ID NO. 84), EGKSSGSGSESKEF (SEQ ID NO. 180), SG3-(SG4)3-SG3-SLQ- YPYDVPDYA (SEQ ID NO. 787), encoded by the nucleotide sequence of SEQ ID NO. 788; DYKDDDDK (SEQ ID NO.789), encoded by the nucleotide sequence of SEQ ID NO. 790; SG3-(SG4)5-SG3-S (SEQ ID NO. 791), encoded by SEQ ID NO. 792; SGGGSGGGGSGGGGSGGGGSYPYDVPDYASGGGS (SEQ ID NO. 793), encoded by SEQ ID NO. 794; GSGATNFSLLKQAGDVEENPGP (SEQ ID NO. 795), encoded by SEQ ID NO.796; SGGGSGGGGSGGGGSGGGGS (SEQ ID NO. 844), encoded by the nucleotide sequence of SEQ ID NO. 845; QLIGMLQGLMRDL (SEQ ID NO. 908), encoded by SEQ ID NO. 909; ASFE (SEQ ID NO. 920), encoded by SEQ ID NO. 921; GS (encoded by GGTTCC), SG (encoded by AGCGGC), EF (encoded by GAGTTC), TS (encoded by ACTAGT), HM (encoded by CACATG), MH (encoded by ATGCAC) or GSG (encoded by GGATCCGGA or GGATCCGGT).

[00277] 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. 929), (G)5 (SEQ ID NO. 930), (G)8 (SEQ ID NO.

931)), 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.

[00278] 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.

[00279] 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.

[00280] 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.

[00281] 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. 932). 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.

[00282] 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.

[00283] 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.

[00284] 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 which are incorporated herein by reference in their entirety.

[00285] 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.

[00286] 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. 846), TATGGCCACAACCATG (SEQ ID NO. 847), AATCTAGATAATACGACTCACTAGAGATCC (SEQ ID NO. 848), TCGCGAATG, TCGCGA, GCTTGCCACAACCCACAAGGAGACGACCTTCC (SEQ ID NO. 849), or ATNFSLLKQAGDVEENPGP (SEQ ID NO. 850, encoded by SEQ ID NO. 851).

[00287] 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

[00288] 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. 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 which are incorporated herein by reference in their entirety.

Polynucleotides

[00289] 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.

[00290] 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*.

[00291] 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.

[00292] 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.

[00293] 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.

[00294] 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.

[00295] 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).

[00296] 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.

[00297] 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.)

[00298] 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.

[00299] 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.

[00300] 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.

[00301] 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.

[00302] 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%).

[00303] 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.

[00304] 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, Mr. Gene (GmBH, Regensburg, Germany) 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.

[00305] 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).

[00306] 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.

[00307] 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.

[00308] 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).

[00309] 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.

[00310] 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.

[00311] 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.

[00312] 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.

[00313] In some embodiments, the compositions of the polynucleotides of the invention may be 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 performed prior to Gibson assembly 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 the steps described 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).

[00314] 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 NOS. 60, 87-88, and/or 878-889, an ecDHFR mutant encoded by nucleotide sequence of SEQ ID NO. 61, 89, 90, and/or 869-877, hDHFR mutant encoded by nucleotide sequence of SEQ ID NO. 91-93, 182-192, SEQ ID NO. 797-832, and/or 890-905.

[00315] In some embodiments, the polynucleotides of the invention may encode effector modules comprising IL2 as the payload comprising the nucleotide sequence of SEQ ID NO. 62-64, or caspase 9 as the payload comprising the nucleotide sequence of SEQ ID NO. 94-102, or FOXP3 as the payload, comprising the nucleotide sequence of SEQ ID NO. 193-202 or luciferase as the payload comprising the nucleotide sequence of SEQ ID NO. 203-208, or BCMA CAR as the payload comprising the nucleotide sequence of SEQ ID NO. 833-835 or Her2 as the payload comprising the nucleotide sequence of 907.

Cells

[00316] 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).

[00317] In some embodiments, cells of the invention may be autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

[00318] 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.

[00319] In some embodiments, cells of the invention may be expanded using expansion factors to trigger proliferation and expansion of the cells. Exemplary expansion factors 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.

[00320] 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.

[00321] In some embodiments, T cells expressing Chimeric antigen receptors or T cells receptors may be further modified to express another one, two, three or more immunotherapeutic

agents of the present invention. The immunotherapeutic agents may be another a cytokine such as IL2, IL12, IL15 and IL18; a regulatory switch; 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.

[00322] In some embodiments, immune cells of the invention may be NK cells modified to express payloads of the invention.

[00323] 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.

[00324] 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).

[00325] 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.

[00326] 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).

[00327] In some embodiments, cells of the present invention may be dendritic cells that are genetically modified to express the compositions of the invention.

[00328] In some embodiments, cells of the invention may be Treg cells. Payloads of the invention may be used to promote the proliferation, survival, activation and /or function of T regulatory cells. Tregs are a distinct population of cells that are positively selected on high affinity ligands in the thymus and play an important role in the tolerance to self-antigens. In addition, T regs have also been shown to play a role in peripheral tolerance to foreign antigens. The ability of Tregs to induce tolerance may be utilized to tune immune responses to the immunotherapeutic agents described herein. Methods for expanding Tregs for immunotherapy have been described by Tang et al., 2004, J. Exp. Med. 199: 1455-65; Battaglia et al., 2005, Blood 105: 4743-48; Earle et al., 2005, Clin. Immunol. 115: 3-9; Godfrey et al., 2004, Blood 104: 453-61; Hoffmann et al., 2004, Blood 104: 895-903.

III. PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

[00329] 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.

[00330] 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.

[00331] 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.

[00332] 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.

[00333] 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.

[00334] 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.

[00335] 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.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] Preferably, the compositions of the invention are administered by injection, e.g., intravenously. When the inventive CAR material is a host cell (or a population thereof) expressing the inventive CAR, the pharmaceutically acceptable carrier for the cells for injection may include any isotonic carrier such as, for example, normal saline (about 0.90% w/v of NaCl in water, about 300 mOsm/L NaCl in water, or about 9.0 g NaCl per liter of water), NORMOSOL R electrolyte solution (Abbott, Chicago, IL), PLASMA- LYTE A (Baxter, Deerfield, IL), about 5% dextrose in water, or Ringer's lactate. In an embodiment, the pharmaceutically acceptable carrier may be supplemented with human serum albumen. Any of the carriers taught in WO2016149578A1 may be useful in the present invention.

IV. APPLICATIONS

[00341] 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).

[00342] 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).

[00343] 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.

[00344] In some embodiments, the safety switches described herein may be useful in the treatment of diseases of protein proliferation and/or protein aggregation e.g. renal diseases and/or neurological diseases such as Alzheimer's diseases, prior diseases etc. In one embodiment, safety switches of the present invention may be expressed in phagocytic cells that are engineered to target aggregated proteins such as amyloid proteins, wherein the safety switches described herein may be used to eliminate the phagocytic cells after the clearance of the aggregated proteins.

1. Adoptive cell transfer (adoptive immunotherapy)

[00345] 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).

[00346] 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 regulate epitope tagged receptors, in APC platforms for stimulating T cells, as a tool to enhance *ex vivo* APC stimulation, to improve methods of T cell expansion, in *ex vivo* stimulation with antigen, in TCR/CAR combinations, in the manipulation or regulation of TILs, in allogeneic cell therapy, in combination T cell therapy with other treatment lines (e.g. radiation, cytokines).

[00347] 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.

[00348] 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 IL2 as payload using SREs of the present invention to reduce the need for preconditioning.

[00349] 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.

[00350] 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).

[00351] 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.

[00352] 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 NOs. 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 NOS. US20150152387A1, U.S. Patent NOS. 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.

[00353] In some instances, sub populations of immune cells may be enriched for ACT. Methods for immune cell enrichment are taught in International Patent Publication NOS. 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. NOS. 9,512,401 (the content of each of which are incorporated herein by reference in their entirety).

[00354] 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 NOS. US 20160298081A1; the contents of which are incorporated by reference herein in their entirety.

[00355] In some embodiments, immune cells may be enriched for FOXP3+ cells to enrich for T cells that are critical for immune tolerance to reduce graft versus host disease.

[00356] 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 NOS. WO2017015427, the content of which are incorporated herein by reference in their entirety.

[00357] 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.

[00358] 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.

[00359] In some embodiments, the T cells of the invention may be separated from peripheral blood by a process known as apheresis, which separates lymphocytes from plasma, platelets and RBCs, and granulocytes. Lymphocyte in peripheral blood cells may further be separated from

monocytes using a semi-automated elutriation device. T cells may also be enriched by magnetic selection with anti CD3/CD28 beads. In one embodiment, an additional step of using a plastic adherent surface to deplete monocytes from the PBMCs may be utilized. Methods of T cell enrichment are disclosed in Stroncek DF et al. (2017) Journal of Translational Medicine.15:59; the contents of which are incorporated by reference in its entirety.

[00360] 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.

[00361] 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 IL2 and a Caspase 9 are linked to the same hDHFR destabilizing domain. The expression of IL2 and Caspase 9 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 IL2 and Caspase 9 constructs are linked to different DDs in two separate effector modules, and 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.

[00362] 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.

[00363] 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.

[00364] 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) into immune cells to promote immune cell proliferation and survival. Transduction of cytokine genes (e.g., gamma-cytokines IL2) into cells will be able to propagate immune cells without addition of exogenous cytokines and cytokine expressing NK cells have enhanced tumor cytotoxicity.

[00365] 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.

[00366] 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).

[00367] 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.

[00368] T cells that are specific to certain tumor antigens, may be subject to chronic antigen exposure. Persistent antigen expression can lead to immune check-point expression, which in turn, induces a state of exhaustion among cognate antigen specific T cells. Constant expression of the chimeric antigen receptors of the invention may result in chronic interaction with the antigen, which leads to exhaustion. The compositions disclosed herein may be used to prevent T cell exhaustion by modulating surface CAR expression using the stimulus specific to the invention. In one embodiment, the SREs of the present invention may be used to achieve pulsatile expression of the compositions of the invention. As used here, "pulsatile" refers to a plurality of payload expression at spaced apart time intervals. Generally, upon administration of the stimulus, the expression of the payload is increased causing the first pulse; following the withdrawal of the stimulus, the expression of the payload decreases and this represents the

interval time between the first exposure and the next exposure to the stimulus, after which the second exposure to the stimulus is initiated.

[00369] Also provided herein, is a method of preventing or reversing T cell exhaustion in a subject in need thereof, where the method comprising administering to the subject a therapeutically effective amount of a composition comprising at least one effector module. In some embodiments, the effector module includes a stimulus response element (SRE) operably linked to at least one immunotherapeutic agent, such that the SRE responds to a stimulus and tunes the expression and/or function of the immunotherapeutic agent, thereby preventing or reversing T cell exhaustion. In some embodiments, the immunotherapeutic agent may be a chimeric antigen receptor. Examples of chimeric antigen receptors include, but are not limited to GD2 CAR, BCMA CAR, CD33 CAR, Her2 CAR, ALK CAR, CD22 CAR, or a CD276 CAR. In some embodiments, the CAR may be a bispecific CAR comprising an extracellular domain which recognizes at least one antigen such as GD2, BCMA, CD33, Her2, ALK, CD22 or a CD276. In some embodiments, the methods described herein may include pulsatile expression of the compositions of the invention to prevent T cell exhaustion. In some instances, T cell exhaustion may be reversed by the addition of the stimulus. In other instances, T cell exhaustion may be reversed by the withdrawal of the stimulus.

[00370] 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

[00371] 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. In one aspect, dendritic cells are modified to express the compositions of the invention and used as cancer vaccines.

[00372] 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 be 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).

[00373] 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 NOS. US20160317633A1, the contents of which are incorporated herein by reference in their entirety.

[00374] Relapse of hematologic malignancies is the primary cause of treatment failure after allogeneic hematopoietic stem cell transplantation (HCT). The Wilm's tumor (WT1) gene product is a tumor associated antigen that is expressed in acute leukemia and other hematological malignancies, with limited expression in normal tissues. The compositions of the present invention may be co-administered with donor derived WT1 peptide loaded dendritic cell vaccine to prevent relapse of disease following immunotherapy (Shah NN et al. (2016) Biol Blood Marrow Transplant. 22(12):2149-215; the contents of which are incorporated herein by reference in their entirety.

3. Combination treatments

[00375] 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 or in conjunction with known immunotherapeutic agents for enhancement of immunotherapy.

[00376] 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 and virosomes.

[00377] 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.

[00378] In some embodiments, immune effector cells modified to expressed biocircuits, effector modules, DDs and payloads of the invention may be combined with cancer vaccines.

[00379] In some embodiments, an effector module comprising a cytokine may be used in combination with an effector module encoding a safety switch or a regulatory switch.

[00380] 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.

[00381] 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.

[00382] 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.

[00383] 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,p'-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.

[00384] 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.

[00385] 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.

[00386] 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.

[00387] 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.

[00388] In some embodiments, CAR-T cells of the invention may be co-administered with retinoids to eradicate myeloid derived suppressor cells. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of early myeloid progenitors, immature granulocytes, macrophages, and dendritic cells at different stages of differentiation. MDSCs have the capacity to suppress both the cytotoxic activities of natural killer (NK) and NKT cells, and the adaptive immune response mediated by CD4+ and CD8+ T cells. Long AH et al. (2016) Cancer Immunol Res.;4(10):869-880 have described the co-treatment of CARs with all trans retinoic acid (ATRA) for the successful treatment of solid tumors (the contents of which are incorporated by reference in its entirety).

[00389] Adjuvant therapy as used herein refers to the treatment that is given in addition to primary therapy to kill any cancer cells, even if the cancer is undetectable by standard laboratory tests. Experimental data have demonstrated that the lymphocyte depletion induced by cytotoxic regimens for the treatment of cancer could contribute to relapse. Relapse to cancer immunotherapy may be minimized by adjuvant immunotherapy. In some embodiments, adjuvant therapy may include the co-administration of recombinant human Interleukin2 in conjunction with dendritic cells pulsed with peptides derived from tumor cells. In some embodiments, dendritic cells pulsed with autologous tumor cell lysate and keyhole limpet hemocyanin (KLH).

Immune cells may be further depleted of CD25 positive T cells. Interleukin 7 may also be co-administered as immunotherapy. In some embodiments, the risk of reinfusing donor- derived tumor cells may be purged with monoclonal antibody 8H9, which interacts with tumor cell surface antigens. Any of the adjuvant therapy methods taught in Merchant et al. (2016), Clin Cancer Res. 1;22(13):3182-91 may be utilized (the contents of which are incorporated by reference in their entirety).

[00390] In some embodiments, compositions of the invention can be combined with CXCR2 inhibitors or anti – CXCR2 antibodies. Highfill SL et al. (2014) found that CXCR2 positive MDSC cells limit the efficacy of immunotherapy by mediating local immunosuppression (Highfill SL, et al. Sci Transl Med. 2014 May 21;6(237):237ra67; the contents of which are incorporated herein by reference in its entirety).

4. Diseases

[00391] 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.

[00392] 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

[00393] 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.

[00394] 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.

[00395] 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.

[00396] 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.

[00397] In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of multiple myeloma such as a CS1 CAR, a CD38 CAR, a CD138 CAR, and a BCMA CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of acute myeloid leukemia such as a CD33 CAR, a CD123 CAR, and a CLL1 CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of T cell leukemia such as a CD5 CAR, and a CD7 CAR. In some embodiments, the CARs of the present invention may be a CAR useful in the treatment of solid tumors such a mesothelin CAR, a GD2 CAR, a GPC3 CAR, a Her2 CAR, an EGFR CAR, a Muc1 CAR, an EpCAM CAR, a PD-L1 CAR, a CEA CAR, a Muc16 CAR, a CD133 CAR, a CD171 CAR, a CD70 CAR, a CLD18 CAR, a cMET CAR, a EphA2 CAR, a FAP CAR, a Folate Receptor CAR, an IL13Ra2 CAR, an MG7 CAR, a PSMA CAR, a ROR1 CAR, and a VEGFR2 CAR.

Infectious diseases

[00398] 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.

[00399] "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

[00400] 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, the respiratory tract, the gastrointestinal tract, and the reproductive tract.

[00401] 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.2015. Science; 350:1084--9; the contents of which are incorporated herein by reference in their entirety). In other embodiments, the microorganisms may be delivered along with immunotherapeutic compositions of the present invention to improve the efficacy of immunotherapy.

6. Tools and agents for making therapeutics

[00402] 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, types of cell, methods of gene transfer, 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

[00403] 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 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), REH, SEM, KOPN8, Daudi, Raji, 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

[00404] 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 payloads such as 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).

[00405] 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.*

[00406] In some embodiments, the preferred reporter moiety may be luciferase proteins. In one embodiment, the reporter moiety is the Renilla luciferase, or a firefly luciferase. Table 14 provides the sequences of the reporter moieties. The amino acid sequences in Table 14 may comprise a stop codon which is denoted in the table with a "*" at the end of the amino acid sequence

Table 14: DD-luciferase constructs

Description	Amino acid sequence	Amino Acid SEQ ID NO.	Nucleic Acid SEQ ID NO.
Linker	EF	-	GAGTTC
Linker	SG	-	AGCGGC
Renilla luciferase	MTSKVYDPEQRKRMITGPQWWARCKQMNVLDSFIN YYDSEKHAENAVIFLHGNAASSYLWRHVVPHIEPVA RCIIPDLIGMGKSGKSGNGSYRLLDHYKYLTAWFELL NLPKKIIFVGHDWGACLAFHYSYEHQDKIKAIVHAES VVDVIESWDEWPDIEEDIALIKSEEGEKMVLENNFFV ETMLPSKIMRKLEPEEFAAYLEPFKEKGEVRRPTLSW PREIPLVKGGKPDVVQIVRNYNAYLRASDDLPKMFIE SDPGFFSNAIVEGAKKFPNTEFVKVKGLHFSQEDAPD EMGKYIKSFVERVLKNEQ	209	217
Firefly Luciferase	MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYAL VPGTIAFTDAHIEVDITYAEYFEMSVRLAEAMKRYGL NTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIY NERELLNSMGISQPTVVFVSKKGLQKILNVQKKLPIIQ KIIIMDSKTDYQGFQSMYTFVTSHLPPGFNEYDFVPES FDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFSHA RDPIFGNQIIPDTAILSVVPFHHGFGMFTTLGYLICGFR VVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKST LIDKYDLSNLHEIASGGAPLSKEVGEAVAKRFHLPGI RQGYGLTETTSAILITPEGDDKPGAVGKVVPFFEAKV VDLDTGKTLGVNQRGELCVRGPMIMSGYVNNPEAT NALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKY KGYQVAPAELESILLQHPNIFDAGVAGLPDDDAGELP AAVVVLEHGKTMTEKEIVDYVASQVTTAKKLRGGV VFVDEVPKGLTGKLDARKIREILIKAKKGGKSKL	210	218
FKBP (F36V, L106P)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGKK VDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQ RAKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPE	11	60, 878-882
FKBP (E31G, F36V, R71G, K105E)	GVQVETISPGDGRTFPKRGQTCVVHYTGMLGDGKK VDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVGQ GAKLTISPDYAYGATGHPGIIPPHATLVFDVELLELE	12	88, 883-889
ecDHFR (R12Y, Y100I)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNT LNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVT WVKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQK LYLTHIDAEVEGDTHFPDYEPDDWESVFSEFHDADA QNSHSYCFEILERR	8	89
OT-Rluc-001 (Renilla Luc - stop)	MTSKVYDPEQRKRMITGPQWWARCKQMNVLDSFIN YYDSEKHAENAVIFLHGNAASSYLWRHVVPHIEPVA RCIIPDLIGMGKSGKSGNGSYRLLDHYKYLTAWFELL NLPKKIIFVGHDWGACLAFHYSYEHQDKIKAIVHAES	211	203

	VVDVIESWDEWPDIEEDIALIKSEEGEKMVLENNFFV ETMLPSKIMRKLEPEEFAAYLEPFKEKGEVRRPTLSW PREIPLVKGGKPDVVQIVRNYNAYLRASDDLPKMFIE SDPGFFSNAIVEGAKKFPNTEFVKVKGLHFSQEDAPD EMGKYIKSFVERVLKNEQ*		
OT-Fluc-002 (Met - FKBP (F36V, L106P) – Linker (EF) – Firefly Luc - stop)	MGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGK KVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVG QRAKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPE EFMEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRY ALVPGTIAFTDAHIEVDITYAEYFEMSVRLAEAMKRY GLNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPAN DIYNERELLNSMGISQPTVVFVSKKGLQKILNVQKKL PIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGFNEYDF VPESFDRDKTIALIMNSSGSTGLPKGVALPHRTACVR FSHARDPIFGNQIIPDTAILSVVPFHHGFGMFTTLGYLI CGFRVVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFF AKSTLIDKYDLSNLHEIASGGAPLSKEVGEAVAKRFH LPGIRQGYGLTETTSAILITPEGDDKPGAVGKVVPFFE AKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNP EATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLI KYKGYQVAPAELESILLQHPNIFDAGVAGLPDDDAG ELPAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLR GGVVFVDEVPKGLTGKLDARKIREILIKAKKGGKSK L*	212	204
OT-Rluc-003 (Met - FKBP (F36V, L106P) – Linker (SG) - Amino acid 2 – 311 of Renilla Luciferase – stop)	MGVQVETISPGDGRTFPKRGQTCVVHYTGMLEDGK KVDSSRDRNKPFKFMLGKQEVIRGWEEGVAQMSVG QRAKLTISPDYAYGATGHPGIIPPHATLVFDVELLKPE SGTSKVYDPEQRKRMITGPQWWARCKQMNVLDSFI NYYDSEKHAENAVIFLHGNAASSYLWRHVVPHIEPV ARCIIPDLIGMGKSGKSGNGSYRLLDHYKYLTAWFE LLNLPKKIIFVGHDWGACLAFHYSYEHQDKIKAIVHA ESVVDVIESWDEWPDIEEDIALIKSEEGEKMVLENNF FVETMLPSKIMRKLEPEEFAAYLEPFKEKGEVRRPTL SWPREIPLVKGGKPDVVQIVRNYNAYLRASDDLPKM FIESDPGFFSNAIVEGAKKFPNTEFVKVKGLHFSQED APDEMGKYIKSFVERVLKNEQ*	213	205
OT-Rluc-004 (ecDHFR (R12Y, Y100I) – Linker (SG) - Amino acid 2 – 311 of Renilla Luciferase - stop)	MISLIAALAVDYVIGMENAMPWNLPADLAWFKRNT LNKPVIMGRHTWESIGRPLPGRKNIILSSQPGTDDRVT WVKSVDEAIAACGDVPEIMVIGGGRVIEQFLPKAQK LYLTHIDAEVEGDTHFPDYEPDDWESVFSEFHDADA QNSHSYCFEILERRSGTSKVYDPEQRKRMITGPQWW ARCKQMNVLDSFINYYDSEKHAENAVIFLHGNAASS YLWRHVVPHIEPVARCIIPDLIGMGKSGKSGNGSYRL LDHYKYLTAWFELLNLPKKIIFVGHDWGACLAFHYS YEHQDKIKAIVHAESVVDVIESWDEWPDIEEDIALIKS EEGEKMVLENNFFVETMLPSKIMRKLEPEEFAAYLEP FKEKGEVRRPTLSWPREIPLVKGGKPDVVQIVRNYN AYLRASDDLPKMFIESDPGFFSNAIVEGAKKFPNTEF VKVKGLHFSQEDAPDEMGKYIKSFVERVLKNEQ*	214	206
OT-Rluc-005 (Renilla Luc - Linker (SG) - FKBP (E31G, F36V, R71G, K105E) - stop)	MTSKVYDPEQRKRMITGPQWWARCKQMNVLDSFIN YYDSEKHAENAVIFLHGNAASSYLWRHVVPHIEPVA RCIIPDLIGMGKSGKSGNGSYRLLDHYKYLTAWFELL NLPKKIIFVGHDWGACLAFHYSYEHQDKIKAIVHAES VVDVIESWDEWPDIEEDIALIKSEEGEKMVLENNFFV ETMLPSKIMRKLEPEEFAAYLEPFKEKGEVRRPTLSW PREIPLVKGGKPDVVQIVRNYNAYLRASDDLPKMFIE SDPGFFSNAIVEGAKKFPNTEFVKVKGLHFSQEDAPD EMGKYIKSFVERVLKNEQSGGVQVETISPGDGRTFPK RGQTCVVHYTGMLGDGKKVDSSRDRNKPFKFMLGK	215	207

	QEVIRGWEEGVAQMSVGQGAKLTISPDYAYGATGH PGIIPPHATLVFDVELLELE*		
OT-Rluc-006 (Renilla Luc - Linker (SG) - ecDHFR (Amino acid 2-159 of WT) (R12Y, Y100I) - stop)	MTSKVYDPEQRKRMITGPQWWARCKQMNVLDSFIN YYDSEKHAENAVIFLHGNAASSYLWRHVVPHIEPVA RCIIPDLIGMGKSGKSGNGSYRLLDHYKYLTAWFELL NLPKKIIFVGHDWGACLAFHYSYEHQDKIKAIVHAES VVDVIESWDEWPDIEEDIALIKSEEGEKMVLENNFFV ETMLPSKIMRKLEPEEFAAYLEPFKEKGEVRRPTLSW PREIPLVKGGKPDVVQIVRNYNAYLRASDDLPKMFIE SDPGFFSNAIVEGAKKFPNTEFVKVKGLHFSQEDAPD EMGKYIKSFVERVLKNEQSGISLIAALAVDYVIGMEN AMPWNLPADLAWFKRNTLNKPVIMGRHTWESIGRP LPGRKNIILSSQPGTDDRVTWVKSVDEAIAACGDVPE IMVIGGGRVIEQFLPKAQKLYLTHIDAEVEGDTHFPD YEPDDWESVFSEFHDADAQNSHSYCFEILERR*	216	208

Animal models

[00407] 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, and HLA transgenic mice.

Cellular assays

[00408] 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.

[00409] 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, PD1, TIM3, 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

[00410] 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.

[00411] 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.

[00412] 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 the Elongation Growth Factor-1. Alpha (EF-1. alpha) promoter. Other constitutive promoters may also be used, including, but not limited to simian virus 40 (SV40)

promoter, the mouse mammary tumor virus (MMTV) promoter, human immunodeficiency virus (HIV) promoter, 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, the 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 the metallothionine promoter, the glucocorticoid promoter, the progesterone promoter, and the tetracycline promoter may be used. In some embodiments, the promoter may be selected from the SEQ ID NO. 220-222, SEQ ID NO. 836.

[00413] 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.

[00414] 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.

[00415] Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the group consisting of the pUC series (Fermentas Life Sciences, Glen Burnie, MD), the pBluescript series (Stratagene, La Jolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, CA). Bacteriophage vectors, such as λGT10, λGT1 1, λZapII (Stratagene), λEMBL4, and λNM1 149, also can be used. Examples of plant expression vectors include pBI01, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-Cl, pMAM, and pMAMneo (Clontech). The recombinant expression vector may be a viral vector, e.g., a retroviral vector or a lenti viral vector. In some embodiments, the vector can be a transposon. Any of the vectors disclosed in the International Patent Publication WO2014065961, may be useful in the present invention (the contents of which are incorporated herein by reference in their entirety).

[00416] 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 the host cell into which the vector is to be introduced.

1. Lentiviral vectors

[00417] 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).

[00418] 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.

[00419] 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.

[00420] 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.

[00421] Cells 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).

[00422] 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.

[00423] 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.

[00424] 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.

[00425] 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.

[00426] 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 NOS. WO2012079000; the contents of each of which are incorporated herein by reference in their entirety).

2. Retroviral vectors (γ-retroviral vectors)

[00427] 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).

[00428] 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 can 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.

[00429] 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.

[00430] 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 NOS. 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).

[00431] 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.

[00432] In some embodiments, polynucleotides encoding the biocircuit, biocircuit components, effector module, and 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.

[00433] 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 NOS. 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)

[00434] 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.

[00435] 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.

[00436] 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.

[00437] 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.

[00438] 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.

[00439] 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.

[00440] 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.

[00441] In some embodiments, more than one effector module or SRE (e.g. DD) may be encoded in a viral genome.

4. Oncolytic viral vector

[00442] 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. NOS. 9,226,977; the contents of which are incorporated by reference in their entirety).

5. Messenger RNA (mRNA)

[00443] 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.

[00444] 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.

[00445] 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

[00446] 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

[00447] 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.

[00448] 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.

[00449] 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.

[00450] 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

[00451] 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.

[00452] 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.

[00453] 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, IL-6, IFN-γ, and TNF-α are elevated.

3. Administration

[00454] 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 are described in U.S. Pat. NOs. 7,435,596; the contents of which are incorporated by reference herein in its entirety.

[00455] 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 which are incorporated herein by reference in their entirety.

[00456] 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.

[00457] 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.

[00458] 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. NOs. EP0930892 A1, the contents of which are incorporated herein by reference.

[00459] 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

[00460] 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.

[00461] 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

[00462] 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.

[00463] *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.

[00464] *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).

[00465] *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.

[00466] *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.

[00467] *Antagonist*: the term "antagonist" as used herein refers to any agent that inhibits or reduces the biological activity of the target(s) it binds.

[00468] *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.

[00469] *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).

[00470] *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.

[00471] *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.

[00472] *Barcode*: the term "barcode" as used herein refers to polynucleotide or amino acid sequence that distinguishes one polynucleotide or amino acid from another.

[00473] *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.

[00474] *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

[00475] *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.

[00476] *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.

[00477] *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.

[00478] *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.

[00479] *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.

[00480] *Feature*: As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[00481] *Formulation*: As used herein, a "formulation" includes at least a compound and/or composition of the present invention and a delivery agent.

[00482] *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.

[00483] *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.

[00484] *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.

[00485] *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.

[00486] *Immunotherapeutic agent:* the term "immunotherapeutic agent" as used herein, refers to the treatment of disease by induction or restoration of the reactivity of the immune system towards the disease with a biological, pharmaceutical, or chemical compound.

[00487] *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).

[00488] *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).

[00489] *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.

[00490] *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.

[00491] *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.

[00492] *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.

[00493] *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.

[00494] *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, like 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).

[00495] *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.

[00496] *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.

[00497] *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.

[00498] *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.

[00499] *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).

[00500] *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.

[00501] *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.

[00502] *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.

[00503] *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).

[00504] *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.

[00505] *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.

[00506] *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.

[00507] *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.

[00508] *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.

[00509] *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

[00510] 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.

[00511] 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.

[00512] 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.

[00513] 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.

[00514] 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.

[00515] 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

[00516] 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.

[00517] 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.

[00518] 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

[00519] 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.

[00520] 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

[00521] 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.

[00522] 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 IL2 expression

[00523] FKBP (L106P) and ecDHFR (R12Y, Y100I) are well-characterized destabilizing domains which can confer instability to fusion partners (e.g., a POI). The instability is reversed by a synthetic ligand named Shield-1 that binds to FKBP DDs and TMP or MTX that binds to DHFR DD. An IL2 polypeptide was linked to either FKBP (F36V; L106P) or ecDHFR (R12Y, Y100I). IL2 constructs were packaged into pLVX-IRES-Puro lentiviral vectors. An IL2 signal sequence was inserted at the N terminus of the construct and linkers were placed between the signal sequence, the DD and IL2.

[00524] OT-IL2-001 (FKBP) was transduced into human colorectal carcinoma line, HCT-116. To measure the dependence of IL2 levels on Shield-1 dose, cells were plated onto a 96 well plate and treated with varying concentrations of Shield-1. Media was then collected from cells and IL2 levels were quantified using IL2 ELISA (Figure 13). IL2 increased with increase in Shield-1 concentration and plateaued at higher Shield-1 dose levels. The half maximal effective concentration or EC_{50} of Shield-1 was determined to be 50 nM.

Example 3. *In vitro* T cell assay development

[00525] The goal of the study was to determine the T cell stimulation regimen and dose of IL12 required 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 14. 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 4. Measuring human T cell responses *in vitro* and *in vivo*

[00526] 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 15A).

[00527] 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 15B).

[00528] 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 15C, 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.

[00529] 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 15D, 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 5. DD regulated luciferase

[00530] A luciferase polypeptide was linked to either FKBP (F36V, L106P or F36V, E31G, R71G, K105E) or ecDHFR (R12Y, Y100I) and cloned into pLVX.IRES. Puro vector.

[00531] DD regulated luciferase can be used to track cells *in vivo* e.g. T cells. Firefly luciferase or Renilla luciferase may be utilized as the payload. HCT-116 cells were stably transduced with the constitutive (OT-RLuc-001) or DD regulated constructs (OT-RLuc-002, OT-RLuc-003, OT-RLuc-004, OT-RLuc-005 and OT-RLuc-006). Cells were treated with 1μM Shield-1, 10μM Trimethoprim or vehicle control for 24 hours and luciferase expression was measured via western blotting using anti-Renilla luciferase and anti-Firefly luciferase antibodies (Abcam, Cambridge, UK). Blots were also probed with anti-GAPDH antibody to ensure uniform protein loading in all samples. As shown in Figure 16A, OT-RLuc-003 showed strong Shield-1 dependent stabilization of Renilla luciferase. OT-RLuc-004, 005 and 006 showed modest stabilization of Renilla luciferase in the presence of their corresponding ligand, while OT-FLuc-002 showed modest stabilization of firefly luciferase with the addition of Shield-1. As expected, the constitutive luciferase construct (OT-RLuc-001) showed expression of Renilla luciferase both in the presence and absence of ligand. (Figure 16A).

[00532] Ligand dependent activity of Renilla and firefly luciferase constructs was measured using coelentrazine and luciferin substrates respectively. Cells were treated with1μM Shield-1, 10μM Trimethoprim, or vehicle control for 24 hours, lysed with assay lysis buffer and incubated with the luciferase substrate. Luciferase activity was measured as luminescence reading using a luminometer and the values were compared to control samples consisting of lysis buffer and substrate. All DD regulated showed ligand dependent increase in luciferase activity compared to control. As expected, the constitutive construct OT-RLuc-001 showed high luciferase activity both in the presence and absence of ligand (Figure 16B).

Example 6. DD regulated IL2 and IL2 mediated functions

[00533] DD-IL2 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 matrigel into mice that 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 and IL2 as well as the ligand levels are measured.

[00534] To evaluate the ability of IL2 expressing cells to form tumors, HCT-116 cells stably transduced with DD-IL2 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 IL2 levels in ligand treated mice compared to untreated controls is indicative conditional regulation of IL2 *in vivo*.

Example 7. DD regulated Caspase 9

[00535] A caspase 9 polypeptide was linked to the N or C-terminus of FKBP, ecDHFR and hDHFR DDs and cloned into pLVX.IRES. Puro vectors.

[00536] To test ligand dependent Caspase 9 production, 1 million HEK-293T cells are plated in a 6-well plate in growth media containing DMEM and 10 FBS and incubated overnight at 37°C, 5% CO2. Cells are transiently transfected with 100ng of DD-Caspase 9 constructs using Lipofectamine 2000 and incubated for 48 hrs. Following the incubation, growth media is exchanged for media containing ligands (Trimethoprim, Methotrexate, or Shield-1, depending on the construct used). Following 24-hour incubation with ligand, cells are lysed and immunoblotted for caspase 9. Increase in Caspase 9 levels with increase in ligand concentrations is indicative of DD mediated regulation of Caspase 9.

Example 8. Evaluation of antitumor response of DD regulated payloads in syngeneic mouse models

[00537] 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-IL2, and DD caspase9. 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 9. Co-expression of DD regulated payloads

[00538] Cells are co-transfected with DD-Interleukin e.g. DD-IL2 and DD Caspase9 or DD FOXP3 constructs. Transfected cells are treated with stabilizing ligands depending on the DD utilized. DD-IL2, expression in the media is measured by ELISA. FOXP3 and caspase 9 expression are evaluated by immunoblotting for FOXP3 and caspase 9 respectively.

Example 10. *In vivo* tracking of DD luciferase cells

[00539] DD luciferase constructs can be utilized as an optical reporter to asses if the ligand and/or the cells expressing the DD constructs reach the targeted tissue. It may also be utilized to study pharmacokinetic and pharmacodynamic (PK/PD) relationships in the context of DD. PK/PD depends on (i) the PK of the stabilizing ligand (ii) behavior of the DD in a specific cell type (iii) cargo protein behavior; some of which may be studied by utilizing the DD regulated luciferase constructs. DD luciferase constructs are expressed or co-expressed in cells of interest such as primary T cells or cell lines e.g. HCT-116, SKOV-3 cells and injected into immune compromised mice e.g. via tail vein, intra peritoneal, or subcutaneous injections. Mice are treated with the corresponding ligand or vehicle control. 8-24 hours following ligand injection, mice are injected with D-Luciferin when the payload is firefly luciferase and Coelentrazin when the payload is Renilla luciferase. Animals are anesthetized and imaged using the Bioluminescence imager (PerkinElmer, Massachusetts). The luciferase output of ligand injected mice is compared to control mice and the signal is quantitated using image analysis software (PerkinElmer, Massachusetts). Luciferase signal is expected to be much higher than background in mice treated with ligand compared to mice treated with vehicle control.

Example 11. Effect of cytokines on immune cell proliferation and activation

[00540] Immune cells such as Natural Killer cells depend on cytokines such as IL2 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.

[00541] 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 IL2 (100

μg/ml). NK-92 cell activation in response to cytokine treatment was evaluated by FACS analysis of a panel of markers whose increased expression is associated with NK activation. These include NKG2D, CD71, CD69; chemokine receptors such as CCR5, CXCR4, and CXCR3, Perforin, Granzyme B and Interferon gamma (IFNg). Prior to FACS for IFNg, cells were cultured for 4 hours with Brefeldin A. IFNg levels were also measured in the media. 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, signalling 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 IL2 treatment for select markers are presented in Table 15.

Table 15: IL2-induced markers

Marker	Fold change
CD69	1.60
CXCR4	3.56
Perforin	1.72
Granzyme	1.62
IFNg (cellular)	1.15
IFNg (Supernatant)	7.43
pAKT (15 mins)	1.23
pAKT (60 mins)	1.34
pSTAT3 (15 mins)	1.19
pSTAT3 (60 mins)	1.38
pSTAT5 (15 mins)	1.90

[00542] Treatment with IL2 resulted in an increase in an increase in the expression of CD69, CXCR4, Perforin, Granzyme B, and IFNg. Further, IFNg levels secreted by NK-92 cells into the media higher than untreated controls upon treatment with IL2. Phosphorylation of STAT5 was increased both at 15 and 60 minutes after the addition of IL2. A modest increase in phospho AKT and STAT3 was observed. Taken together, these results show that cytokines can activate NK cells.

[00543] The dependency of immune cells on cytokines for proliferation was tested in NK-92 cells (natural killer cell line) and T cell lines Jurkat cells and SupT1 cells. Cells were seeded at 40,000 per well and cultured in the presence of IL2 or IL15 for 3 days. The number of NK-92 cells decreased with time in the untreated cells. However, treatment with IL2 increased cell

numbers. In contrast, the cell numbers obtained with cytokine treatment in SupT1 and Jurkat cells was comparable to the untreated control. Thus, NK-92 cells depend on cytokines for survival.

Example 12. DD regulated FOXP3 expression

[00544] A fusion molecule is generated by fusing full length or truncated (FOXP3Δ2) and DDs such as ecDHFR (DD) or FKBP (DD). These fusion molecules were cloned into pLVX-IRES-Puro vectors.

[00545] To test ligand dependent FOXP3 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 transfected with the constructs using Lipofectamine 2000 and incubated for 24 hrs. Following the incubation, media was exchanged for growth medium with or without 10μM Trimethoprim or 1μM Shield-1 and further incubated for 24 hrs. Cells were harvested and FOXP3 levels were analyzed via western blotting using anti FOXP3 antibody (Abcam, Cambridge, UK). OT-FOXP3-003, and OT-FOXP3-007 showed the strongest Shield-1 dependent stabilization of FOXP3, while OT-FOXP3-008 showed the strongest Trimethoprim dependent stabilization of FOXP3 (Figure 17A and Figure 17B). Constructs OT-FOXP3-004 and OT-FOXP3-009 showed modest TMP and shield-1 dependent stabilization.

Example 13. Effect of ligand on T cell proliferation

[00546] 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 with control vehicle (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 14. Promoter selection for expression of SREs in T cells

[00547] The expression of SREs expressed in a vector can be driven either by 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. 223) 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 18, both the CMV promoter and the EF1a promoter can drive the expression of GFP in SupT1 cells and T cells. The percentage of GFP positive T cells was higher when the 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 compared to the CMV promoter. Thus, the optimum promoter suitable for expression differs based on the cell type.

Example 15. EBV tumor antigen mediated TCR re-stimulation *invivo*

[00548] Human T cells engineered to express DD regulated cytokines are not antigen specific. However, functionality of T cells *in vivo* requires their restimulation which occurs upon engagement with the antigen. This requirement for antigen mediated restimulation can be mimicked *in vivo* in mice, the Epstein Barr Virus (EBV) antigen may be utilized. Approximately 90% adults have a current or a previous EBV infection. Additionally, the major histocompatibility group HLA-A02 has been associated with the decreased risk of developing EBV positive Hodgkin's lymphoma, suggesting that the CTL peptide epitopes that promote viral clearance are presented by HLA-A02. Several tumor cell lines that are HLA-A02 positive, e.g. Raji cells, are used for *in vivo* studies. Primary human T cells obtained from various donors are expanded with CD3/CD28 dynabeads. To test reactivity of T cells the EBV antigen, EBV positive Raji cells and EBV negative Ramos cells are used. The involvement of HLA-A02 in antigen recognition is tested using anti-HLA antibodies to test assay specificity. Cell killing assays are performed by incubating T cells with fluorescently labelled Raji cells or Ramos cells and the ability of the donor T cells to preferentially kill Raji cells is evaluated. The activation of T cells in response to interaction with EBV antigen is measured by culturing mitomycin treated Raji or Ramos cells with fluorescently labelled T cells. The activation and proliferation status of T cells is examined by measuring expression of IFNg, CD107a, Granzyme, and Perforin. Since most humans have been exposed to EBV, the donor T cells in most instances are expected to be immunoreactive to Raji cells, but not Ramos cells. It is likely that T cells reactive to Raji cells will be positive for markers of T cell activation such as Granzyme and Perforin.

Example 16. Ligand dependent IL2 stabilization *in vivo*

[00549] An IL2 polypeptide was linked to either FKBP (F36V; L106P) or ecDHFR (R12Y, Y100I). IL2 constructs were packaged into pLVX-IRES-Puro lentiviral vectors. An IL2 signal sequence was inserted at the N terminus of the construct and linkers were placed between the signal sequence, the DD and IL2.

[00550] OT-IL2-001 (FKBP) was transduced into human colorectal carcinoma line, HCT-116. IL2 expression *in vitro* was confirmed by ELISA. To test *in vivo* ligand mediated regulation, 5 million HCT 116 cells transduced with IL2 constructs were injected subcutaneously into the flanks of immunocompromised mice. Approximately, two weeks after injection, when the tumors reach a size of approximately 300 cubic mm, mice are dosed with corresponding stabilizing ligands or corresponding vehicle control. Shield-1 is injected with a carrier consisting of 10%Dimethylacetamide, 10% Solutol HS15, and 80% saline at a concentration of 10mg/kg body weight. Mice were euthanized at tumor and plasma samples were collected and analyzed for IL2 levels. Tumor IL2 levels were measured by ELISA as picograms per mg of protein. As shown in Figure 19, tumor IL2 levels detected with Shield-1 treatment was higher than levels detected with vehicle control. These data demonstrate a dose dependent IL2 secretion from HCT116 cells stably expressing FKP-IL2 *in vivo*.

Example 17. Optimization of T cell transduction and expansion

[00551] The T cell expansion and transduction protocol consists of stimulating donor derived human T cells on day zero with aCD3/aCD28 bead stimulation to promote T cell proliferation. On day one, T cells were transduced with the construct of choice and expanded for up to day 11 with occasional media changes. On day 11, the beads were washed out and the cells were frozen in aliquots for use in various functional assays. The process of T cell expansion and transduction requires optimization to ensure the exponential proliferation of T cells, following the initial 4-day lag in growth of the T cells which is caused by the viral transduction. Unoptimized expansion protocol may result in static growth for up to 10 days requiring instead 21 days to achieve similar expected T cell number and a concomitant reduction in viability and abnormal CD4 to CD8 T cell ratio. The source of αCD3/αCD28 used for T cell stimulation and the ratio of the beads were tested to identify optimal conditions. αCD3/αCD28 beads from different sources were utilized. These included dynabeads (ThermoFisher, Waltham, MA), CD3/CD28 +/- CD2 with anti-Biotin MACSiBead (Miltenyi Biotec, Germany), Macrobeads – 3μm magnetic polymer beads with αCD3/αCD28 antibody coating, soluble tetrameric antibody complexes of

αCD3/αCD28 (StemCell, Canada). Bead and T cells were mixed at 3:1, 1:1, 1:3 and 1:9 ratios to identify optimal ratios for co-culture. Assays were also performed using two separate donors to account for donor related variabilities. Percentage cell viability was measured at 0, 4 and 7 days. As shown in Figure 20, both donors showed improved cell viability counts at 1:3 bead to cell ratio compared to all other conditions, especially at day 4. One of the donors also showed improved cell viability at with 1:9 bead to cell ratio. Cell number counts were performed using both the cellometer and flow cytometry analysis. For this analysis, cells were infected with viruses at MOI of 10 and compared to mock (Lentiboost (LB) transduced cells to examine the effects of viral transduction on T cell counts. The fold change in cell growth at day 4 and day 7 compared to growth at day 0 was analyzed and the results from the cellometer counts are represented in Table 16.

Table 16. T cell proliferation

Experimental condition	Donor1		Donor 2	
	Day 4	Day 7	Day 4	Day 7
MOI 3:1	1.70	5.00	1.94	3.90
MOI 1:1	2.15	3.95	2.55	4.30
MOI 1:3	1.69	4.25	2.75	8.80
MOI 1:9	1.65	3.70	3.91	6.35
MOI Immuno Cult	0.98	2.30	0.95	3.05
LB 3:1	2.10	4.25	1.45	5.00
LB 1:1	2.20	6.35	2.35	6.65
LB 1:3	2.05	9.45	2.97	10.50
LB 1:9	1.55	5.60	2.77	3.75
LB Immuno Cult	1.05	3.10	0.86	2.30

[00552] As shown in Table 16, the overall proliferation in both donors was greater at day 7 than at day 4. For donor 1, the proliferation at day 4 among the virally transduced cells was highest when an MOI of 10 was used in conjunction with a bead to cell ratio of 3:1, while donor 2 T cells proliferated the most at a ratio of 1:9. At day 7, 1:1 ratio for donor 1 and 1:3 ratio for donor 2 showed highest cell proliferation. Based on these results a bead to cell ratio of 1:3 was identified as optimal for promoting T cell proliferation.

[00553] T cells transduced at various multiplicity of infection (MOI) were also tested using flow cytometry. The results for donor 1 are shown in Table 17.

Table 17. Effect of viral titer and bead to cell ratio

MOI	Bead to cell ratio				Immunocult
	3:1	1:1	1:3	1:9	
10 MOI	0.81	0.93	0.85	1.28	1.42
2 MOI	0.37	0.50	0.51	1.00	0.65
0.4 MOI	0.33	0.46	0.50	0.72	0.86

[00554] As shown in Table 17, bead ratio of 1: 9 showed the highest cell viability among all conditions tested for donor1. Similar results were obtained for donor 2.

[00555] Ratio of CD4 to CD8 within the proliferating T cell populations. At the start of the experiment, the CD4 to CD8 ratio was determined to be 3 and the skewing of populations. The results are shown in Table 18.

Table 18. CD4 to CD8 cell ratio

MOI	**Donor 1**					**Donor 2**				
	3:1	**1:1**	**1:3**	**1:9**	**Immunocult**	**3:1**	**1:1**	**1:3**	**1:9**	**Immunocult**
10	8.63	8.73	5.84	3.7	7.44	4.53	3.25	2.56	1.65	2.75
2	9.6	9.91	7.18	4.11	6.45	5.25	3.16	2.04	1.56	3.23
0.4	10.85	11.33	7.51	4.23	5	6.22	4.71	2.59	1.43	3.55
LB	6.95	7.24	5.24	3.21	4.96	3.86	3.27	2.18	1.23	2.78

[00556] Donor 1 showed CD4 to CD8 ratio close to 3 when a bead to cell ratio of 1:9 was used. Similar results were obtained for donor 2 when a bead to cell ratio of 1:3 was used.

[00557] Taken together, these experiments show that activation induced cell death may occur when T cells are overstimulated by beads, and therefore optimal bead to T cell ratio is required. The experiments suggest that the optimal bead to cell ratio was 1:3 across various MOIs.

Example 18. Analysis of BCMA CAR expression

[00558] A BCMA CAR fusion polypeptide was linked to either to the N terminus of the FKBP-DD, ecDHFR-DD or human DHFR-DD and the constructs were cloned into pLVX-IRES-Puro vector under the transcriptional control of EF1a promoter.

[00559] To test ligand dependent expression of DD-BCMA CAR constructs, 1 million HEK HCT116 cells were cultured in growth medium containing DMEM and 10% FBS and transfected with CAR constructs using Lipofectamine 2000 or LentiBoost. 48 hours after transfection, cells were treated with 1μM or10μM Shield-1, 10μM Trimethoprim, 1μM Methotrexate, or vehicle control and incubated for 24 hours. Surface expression of DD-BCMA CAR constructs in HCT116 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). As shown in Figure 21, surface expression of OT-BCMA-002 with FKBP-DD was elevated in the presence of Shield-1, while OT-BCMA-003 with ecDHFR-DD showed elevated surface expression in the presence of Trimethoprim. As expected, constitutively expressed construct OT-BCMA-001 showed high expression even in the absence of ligand.

Example 19. Analysis of CAR expression and function

[00560] The expression of chimeric antigen receptors described herein such as, but not limited to CD22 CAR, ALK CAR, CD33 CAR, HER2 CAR and GD2 CAR constructs are fused to destabilizing domains such as ecDHFR DD, FKBP DD and hDHFR DDs. To test ligand dependent expression of the constructs, immune cells are cultured in growth medium containing DMEM and 10% and transduced are transduced with the CAR constructs. 48 hours after transduction, cells are treated with the ligand corresponding to the DD such as 1μM or10μM Shield-1, 10μM Trimethoprim, 1μM Methotrexate, or vehicle control and incubated for 24 hours. Cells are then analyzed by western blot using the CD3 Zeta, a component of the CAR. Surface expression of the CAR is analyzed by FACS using Protein L. Intracellular and surface expression of CARs is expected to be undetectable in the absence of ligand, but strongly induced by the presence of the ligand.

[00561] The efficacy of T cells expressing DD regulated CAR constructs in functionally interacting with target cells is evaluated. To interact with the CAR T cells, the chosen target cells express the antigen related to the CAR either naturally or ectopically. For example, target cells which have high endogenous expression of BCMA include KMS11, MM-1S, RPMI-8226 cells; target cells expressing CD33 include HL-60, MOLM13, MOLM14 cells. Alternatively, target

cell lines may be engineered to ectopically express the antigen in cell lines that have low endogenous expression of the antigen.

[00562] Multiple assays are used to measure functionality. Prior to co culture, the target cells are optionally cultured in the 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 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 CAR expressing T cells are co cultured with antigen expressing target cells in the presence of ligand. Cytotoxicity is not expected in vehicle control cells or when the target cells do not express the antigen are utilized.

[00563] Cytolytic potential of DD 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 CAR and mock transduced cells are co-incubated with cognate antigen 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 CAR are expected to demonstrate specific cytolysis only in the presence of ligand. Cells with DDCAR in the absence of ligand or mock transfected cells are expected to show minimal cytolytic activity.

[00564] 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.

[00565] Engagement of the CAR with its cognate antigen results in the activation of T cells 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 CAR expressing T cells are co cultured with cognate antigen expressing target cells in the presence of

ligand. Both parameters are not expected in to change in vehicle control cells or when the target cells do not express antigen are utilized.

[00566] To measure the ability of DD regulated CARs to promote tumor-free survival, mice are injected intravenously with antigen positive target cells. Following injections, mice are treated with untransduced mock T cells or T cells that are transduced with antigen specific chimeric antigen receptors. Mice are then split into two cohorts; one cohort is treated with the ligand specific to the SRE and the second cohort which is treated with the vehicle control. Survival of the mice is monitored for up to 80 days after the administration of target cells. Tumor bearing mice treated with CAR transduced T cells and the ligand, are expected to survive longer than mice treated with untransduced cells; vector control transduced T cells or vehicle control.

[00567] To measure ligand induced reduction in tumor growth, mice are injected orthotopically with antigen positive target cells on day 0. The mice are then treated with cyclophosphamide intraperitoneally on day 3. Cells are treated with antigen specific CAR construct. The mice are treated with recombinant interleukin 7 or interleukin 7 complexed with IL7 antibody, two-three times a week for three weeks to promote T cell persistence. Mice are then split into two cohorts; one cohort is treated with the ligand specific to the SRE and the second cohort which is treated with the vehicle control. The size of the tumors is measured at various time points after inoculation. Mice treated with antigen specific CAR and the ligand are expected to be tumor free while mice treated with mock transduced cells, or vehicle controlled cells are predicted to succumb to the tumors

[00568] To test if DD regulated CARs can cause regression of established tumors in a ligand dependent fashion, mice are orthotopically inoculated with antigen positive T cells expressing luciferase. Tumors are allowed to grow for 8 days, and the growth is monitored using bioluminescent imaging. On day 8, after tumor inoculation, CAR transduced cells are injected intravenously with or without cytokine and cytotoxic therapy augmentation. Concurrent ligand or vehicle control treatment is also initiated. Mice treated with CAR T cells are expected to show tumor regression and long term disease control in the presence of ligand, whereas all mice treated with mock transduced cells are expected to succumb to progressive tumor growth.

Example 20. Measuring T cell exhaustion phenotype and its reversal

[00569] Primary T cells are activated using soluble CD3/CD28 or CD3/CD28 dynabeads. 24 hours later, cells are transduced with DD regulated CD19 CAR constructs and allowed to rest for 24 hours. Cells are then treated with the ligand specific to the SRE or vehicle control. At day 4, the CD3/CD28 beads are removed and the cells are cultured for another 3 days. At day 7, cells

are washed extensively to remove the ligand and replated in the absence of the ligand and cultured for 3 days. At day 10, cells were washed and replated in the absence of ligand. A sample of the cells are analyzed at day 10 for phenotypic and functional markers associated with exhaustion. The rest of the cells are cultured for 3 days in the absence of ligand and analyzed for phenotypic and functional exhaustion markers at day 14. T cells cultured for the duration of the experiment either in the presence or absence of ligand are included as controls. Phenotypic markers for exhaustion such as PD1, TIM3, LAG3, BTLA, CD160, 2B4, and CD39a are measured both in CD4 and CD8 T cell populations. Since chronic T cell activation has been shown to result in T cell exhaustion, T cells cultured under the continuous presence of ligand throughout the experiment are expected to be positive for multiple markers of exhaustion. T cells cultured in the absence of ligand throughout the experiment are expected to negative for multiple markers of exhaustion, since the expression of the CAR will be undetectable/low in the absence of ligand. At day 10, cells where the ligand is removed at day 7 are expected to have a lower percentage of cells that are positive for multiple exhaustion markers when compared to cells that have been treated with ligand throughout the duration of the experiment. This result is expected in both CD8 and CD4 population of T cells.

Example 21. Dual specific chimeric antigen receptor

[00570] Human T cells are transduced with a lentiviral vector encoding dual specific chimeric antigen receptors. Dual specific CARs targets include, but not limited to GD2, CD33, BCMA, Her2, ALK, CD22 and CD276. Cells are cultured in the presence of ligand or vehicle control for 24-48 hours. Additional controls such as human T cells that are mock transduced or transduced with a vector encoding septicity to one antigen only are included. CAR expression is evaluated by flow cytometry using anti-idiotype CAR antibody. Expression of dual specific CAR is expected only in cells transduced with dual specific CAR construct in the presence of ligand, while the controls transduced with the CAR constructs showing single specificity are expected to show expression of the single CAR construct, and in the presence of ligand.

[00571] T cells are also analyzed for proliferation, markers of apoptosis and memory phenotype. Cells are cultured per methods described above. Ligand is removed either at day 7 or day 10 and cells are analyzed at day 14 for apoptosis using Annexin V staining and for the memory phenotype using CD62L as the marker. When compared to untreated cells, cells continuously treated with ligand are expected to show an increase in apoptotic cells, a decrease in proliferation and a decrease in CD62L expression, which are indicative of T cell exhaustion.

Ligand withdrawal at day 7 or day 10 is expected to show low Annexin V and high CD62L expression, and an increase in proliferation similar to untreated cells.

Example 22. Measuring T cell exhaustion phenotype and its reversal

[00572] Primary T cells are activated using soluble CD3/CD28 or CD3/CD28 dynabeads. 24 hours later, cells are transduced with DD regulated CD19 CAR constructs and allowed to rest for 24 hours. Cells are then treated with the ligand specific to the SRE or vehicle control. At day 4, the CD3/CD28 beads are removed and the cells are cultured for another 3 days. At day 7, cells are washed extensively to remove the ligand and replated in the absence of the ligand and cultured for 3 days. At day 10, cells were washed and replated in the absence of ligand. A sample of the cells are analyzed at day 10 for phenotypic and functional markers associated with exhaustion. The rest of the cells are cultured for 3 days in the absence of ligand and analyzed for phenotypic and functional exhaustion markers at day 14. T cells cultured for the duration of the experiment either in the presence or absence of ligand are included as controls. Phenotypic markers for exhaustion such as PD1, TIM3, LAG3, BTLA, CD160, 2B4, and CD39a are measured both in CD4 and CD8 T cell populations. Since chronic T cell activation has been shown to result in T cell exhaustion, T cells cultured under the continuous presence of ligand throughout the experiment are expected to be positive for multiple markers of exhaustion. T cells cultured in the absence of ligand throughout the experiment are expected to be negative for multiple markers of exhaustion, since the expression of the CAR will be undetectable/low in the absence of ligand. At day 10, cells where the ligand is removed at day 7 are expected to have a lower percentage of cells that are positive for multiple exhaustion markers when compared to cells that have been treated with ligand throughout the duration of the experiment. This result is expected in both CD8 and CD4 population of T cells.

[00573] T cells are also analyzed for proliferation, markers of apoptosis and memory phenotype. Cells are cultured per methods described above. Ligand is removed either at day 7 or day 10 and cells are analyzed at day 14 for apoptosis using Annexin V staining and for the memory phenotype using CD62L as the marker. When compared to untreated cells, cells continuously treated with ligand are expected to show an increase in apoptotic cells, a decrease in proliferation and a decrease in CD62L expression, which are indicative of T cell exhaustion. Ligand withdrawal at day 7 or day 10 is expected to show low Annexin V and high CD62L expression, and an increase in proliferation similar to untreated cells.

Example 23. Functional analysis of reversal of T cell exhaustion

[00574] The functionality of T cells expressing DD regulated CAR constructs is evaluated by measuring cytokine release. T cells expressing DD CAR constructs are co cultured with target cells expressing the antigen (endogenously or ectopically). T cells are activated at day 0 using CD3/CD28 beads. 24 hours later, cells are transduced with DD regulated CAR constructs and allowed to rest for 24 hours. Cells are then treated with the ligand specific to the SRE or vehicle control. At day 4, the CD3/CD28 beads are removed and the cells are cultured for another 3 days. At day 7, cells are washed extensively to remove the ligand and replated in the absence of the ligand and cultured for 3 days. In an additional experimental condition, cells are treated with ligand till day 10 instead of day 7. T cells cultured for the duration of the experiment either in the presence or absence of ligand are included as controls. Supernatant was collected from cells after 24 hours and IL2 and IFNg levels were measured as a read out of T cell function. When compared to untreated cells, cells continuously treated with ligand are expected to show an increase in IL2 and IFNg expression at day 14, which are indicative of functional T cells. Ligand withdrawal at day 7 or day 10 is expected to minimally affect the levels of IFNg and IL2 levels.

[00575] The ability of biocircuits of the invention to functionally rescue the exhausted T cells is also evaluated. T cells treated with ligand till day 10 are sorted and selected for cells that are positive for chimeric antigen receptor as well as multiple exhaustion makers (e.g. PD1, TIM3, LAG3). The cells are divided into two groups, one group is treated with ligand, while the second group is treated with vehicle control. Functionality of T cells is measured using IL2 levels as a surrogate. Ligand withdrawal is predicted to reverse T cell exhaustion, and hence cells subject to ligand withdrawal at day 10 are expected to have higher IL2 levels compared to ligand treated cells.

Example 24. Optimizing biocircuit behavior

[00576] The biocircuits of the invention comprise multiple modules which can be optimized. Libraries of each of the components is generated to allow for the rapid generation of new constructs with desired behaviors. Ligand pharmacokinetics is a powerful tool for payload specific tuning *in vivo,* which can be used to shift the ligand response curve of the effector module to the left or right depending on the modulating factors. Several modulating factors are tested, including, but not limited to the ligand dose, concentrations, magnitude, duration, and route of administration. Destabilizing domains can also be modified to improve biocircuit behavior. The destabilizing domain is the core determinant of the dynamic range of the biocircuit. Depending on the DD selected, the ligand response curve of the effector module can

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be shifted up or down. The nature, position of the DD within the effector module as well as the number of DDs within an effector module are modified. DD selection is also altered depending on its degradation kinetics desired. Promoters that transcriptionally control the expression of the SREs are optimized. Choice of promoter impacts the basal-off state and affects the dynamic range of stabilization. Further, promoter choice contributes to the extent of stabilized payload produced. Other optimizable elements of the biocircuits include vector, translational elements, leader sequence, placement of the components within the SRE, codon selection, protease sites, linkers, and mRNA stability.

[00577] While the present invention has been described at sonme 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 interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

[00578] 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.

[00579] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers or steps.

[00580] The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition for inducing an immune response in a cell or a subject comprising a first effector module, said effector module comprising a destabilizing domain (DD) operably linked to at least one immunotherapeutic agent, wherein said at least one immunotherapeutic agent comprises a chimeric antigen receptor (CAR) selected from a GD2 CAR, a Her2 CAR, a BCMA CAR, a CD33 CAR, an ALK CAR, a CD22 CAR, and a CD276 CAR, and wherein the DD is derived from a human DHFR (hDHFR) comprising the amino acid sequence of SEQ ID NO. 2 or a mutant hDHFR having one, two, three or more amino acid mutations compared to said hDHFR.

2. The composition of claim 1, wherein the DD is responsive to or interacts with at least one stimulus.

3. The composition of claim 1, wherein DD comprises a mutant hDHFR protein having at least one mutation selected from 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, 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.

4. The composition of claim 3, wherein the stimulus is selected from Trimethoprim (TMP) and Methotrexate (MTX).

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5. The composition of claim 1, wherein the CAR comprises an extracellular moiety, a transmembrane domain, an intracellular signaling domain, and optionally, one or more co-stimulatory domains.

6. The composition of claim 5, wherein the CAR is designed as 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.

7. The composition of claim 6, wherein the extracellular target moiety is selected from any of:

i. an Ig NAR,
ii. a Fab fragment,
iii. a Fab' fragment,
iv. a F(ab)'2 fragment,
v. a F(ab)'3 fragment,
vi. an Fv,
vii. a single chain variable fragment (scFv),
viii. a bis-scFv, a (scFv)2,
ix. a minibody,
x. a diabody,
xi. a triabody,
xii. a tetrabody,
xiii. an intrabody,
xiv. a disulfide stabilized Fv protein (dsFv),
xv. a unibody,
xvi. a nanobody, and
xvii. an antigen binding region derived from an antibody that specifically binds to any of a protein of interest, a ligand, a receptor, a receptor fragment or a peptide aptamer.

8. The composition of claim 6, wherein the extracellular target moiety is selected from an ALK target moiety, comprising the amino acid sequence of SEQ ID NO.242- 257 and 422-429, a CD22 target moiety, comprising the amino acid sequence of SEQ ID NO.258-262 and 430-432, a CD276 target moiety, comprising the amino acid sequence of SEQ ID NO. 263-270 and 433-436, a GD2 target moiety, comprising the amino acid sequence of SEQ ID NO.271-349

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and 437-465, a CD33 target moiety, comprising the amino acid sequence of SEQ ID NO. 350-357, a BCMA target moiety, comprising the amino acid sequence of SEQ ID NO. 358-365, and a Her2 target moiety, comprising the amino acid sequence of SEQ ID NO. 366-421 and 466-473.

9. The composition of claim 6, wherein

(a) the intracellular signaling domain of the CAR is the signaling domain derived from T cell receptor CD3zeta or 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; and

(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.

10. The composition of claim 6, wherein the transmembrane domain comprises the amino acid sequence of SEQ ID NO. 527-624.

11. The composition of claim 6, wherein the transmembrane domain further comprises a hinge region comprising the amino acid sequence of SEQ ID NO.628-694.

12. The composition of any of claims 1-11 wherein said first effector module comprises one or more of:

(a) a BCMA CAR-DD, comprising the amino acid sequence of any of SEQ ID NOs. 775-777, and/or

(b) a HER2-DD, comprising the amino acid sequence of SEQ ID NO. 906.

13. A polynucleotide encoding the effector molecule of any one of the compositions of claims 1-11.

14. The polynucleotide of claim 13, wherein the polynucleotide is a DNA molecule, or a RNA molecule.

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15. The polynucleotide of claim 14, wherein the polynucleotide is RNA and said RNA is a messenger RNA.

16. The polynucleotide of claim 15, which is chemically modified.

17. The polynucleotide of claim 14, which comprises spatiotemporally selected codons.

18. The polynucleotide of claim 15, wherein the polynucleotide encodes at least one additional feature selected from a promoter, a linker, a signal peptide, a tag, a cleavage site and a targeting peptide.

19. A vector comprising a polynucleotide of any of claims 13-18.

20. The vector of claim 19 wherein the vector is a viral vector, or a plasmid.

21. The vector of claim 20, wherein the vector is a viral vector and said 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, wherein the polynucleotide encodes any of the compositions of claim 1-22.

23. An immune cell for adoptive cell transfer (ACT), which expresses any of the compositions of any of claims 1-12, the polynucleotides of any of claims 13-18, and/or is infected or transfected with the vector of any of claims 30-33.

24. The immune cell of claim 23, wherein the immune 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.

25. The immune cell of claim 24, which is autologous, allogeneic, syngeneic, or xenogeneic in relation to a particular individual subject.

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26. A method of reducing a tumor volume or burden in a subject comprising contacting the subject with compositions of any of claims 1-12, the polynucleotides of any of claims 13-18, the vector of any of claims 19-22 or the immune cells of any of claims 23-28.

27. A method of providing an anti-tumor immune response in a subject comprising providing to the subject an effective amount of the compositions of any of claims 1-12, the polynucleotides of any of claims 13-18, the vector of any of claims 19--22 or the immune cells of any of claims 23-25.

28. A method of inducing an immune response in a subject comprising providing to the subject an effective amount of any of the compositions of claims 1-12, the polynucleotides of any of claims 13-18, the vector of any of claims 19-22 or the immune cells of any of claims 34-38.

29. A method of preventing or reversing T cell exhaustion in a subject in need thereof, the method comprising providing to the subject, a therapeutically effective amount of compositions of any of claims 1-12, the polynucleotides of any of claims 13-18, the vector of any of claims 19-22 or the immune cells of any of claims 23-25, wherein the DD responds to a stimulus and tunes the expression and/or function of the immunotherapeutic agent, thereby preventing or reversing T cell exhaustion.

30. The method of claim 29, wherein the immunotherapeutic agent is a chimeric antigen receptor.

31. A method of detecting the presence of cancer in a mammal, comprising the steps of:

(a) contacting a sample comprising one or more cells from the mammal with the compositions of any of claims 1-12, the polynucleotides of any of claims 13-18, the vector of any of claims 19-22 or the immune cells of any of claims 23-25 and

(b) detecting the complex, wherein the detection of the complex is indicative of the presence of cancer in the mammal.

Figure 1

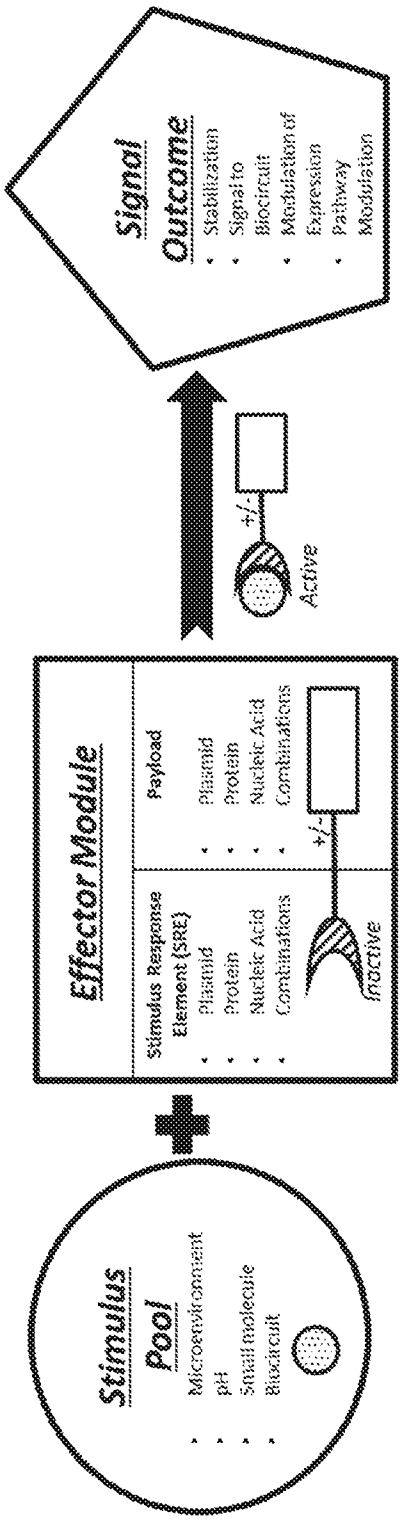

Signal Outcome
Stabilization
Signal to Biocircuit
Modulation of Expression
Pathway Modulation
+/-
Active
Effector Module
Stimulus Response Element (SRE)
Plasmid
Protein
Nucleic Acid
Combinations
Payload
Plasmid
Protein
Nucleic Acid
Combinations
+/-
Inactive
Stimulus Pool
Microenvironment
pH
Small molecule
Biocircuit

Figure 2

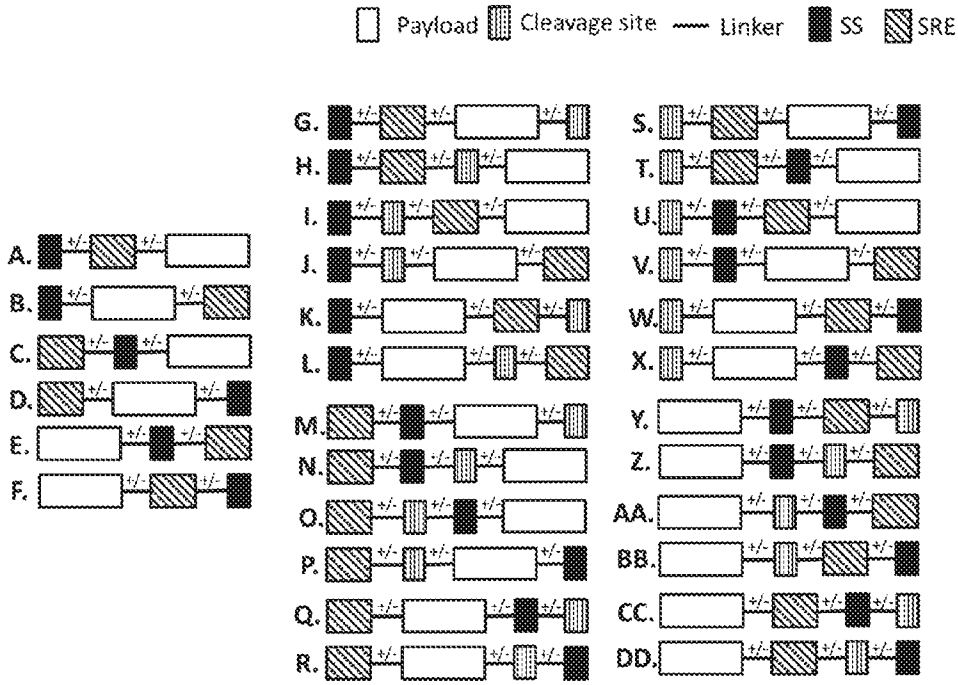


Figure 3

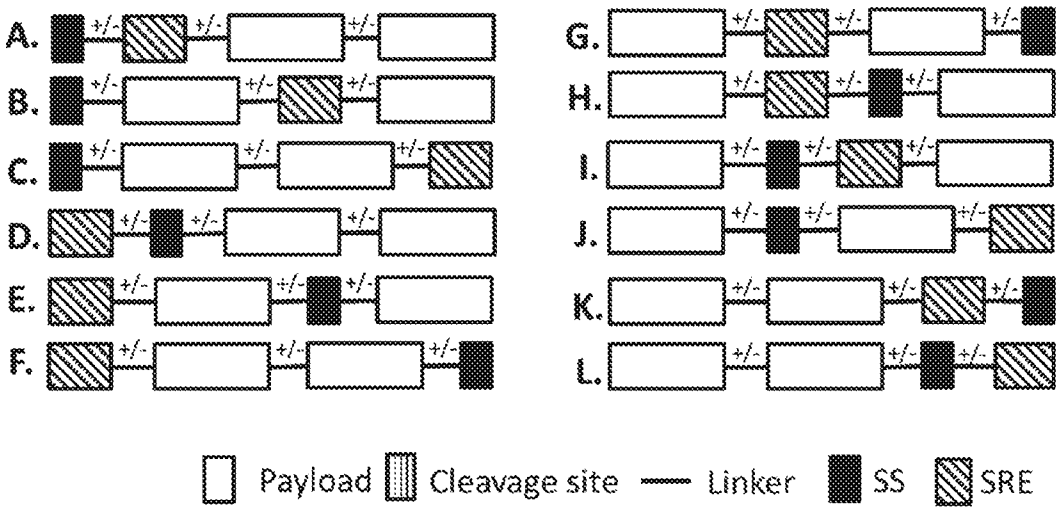
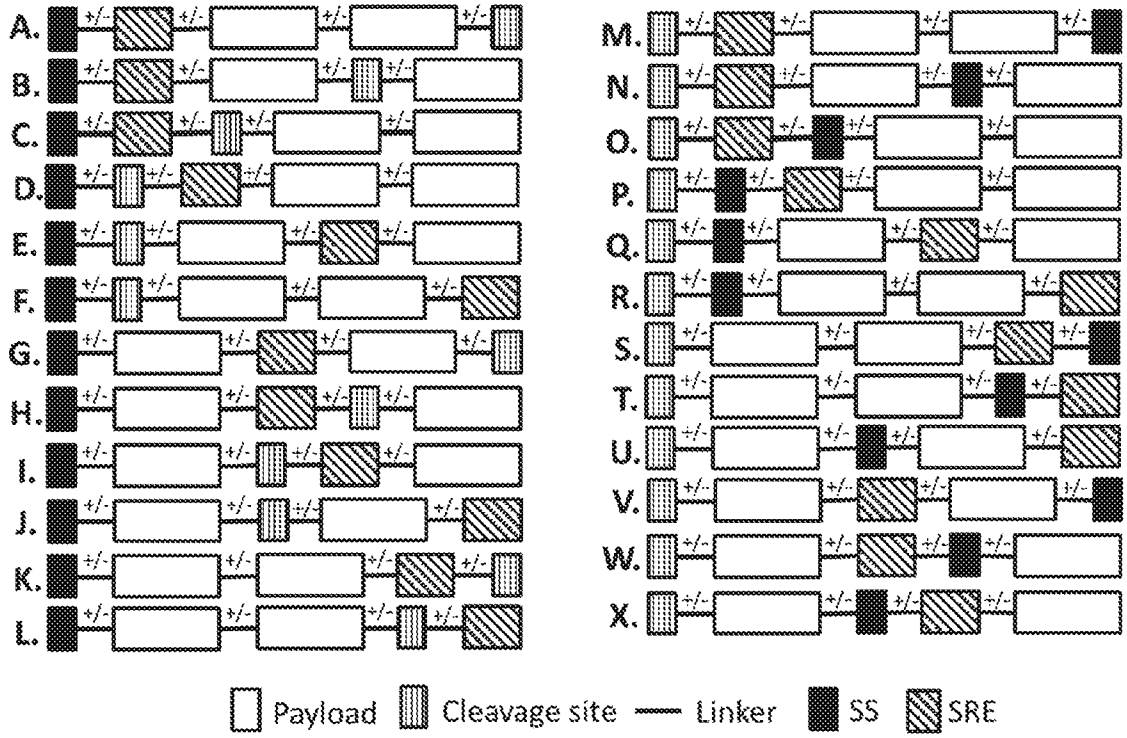


Figure 4



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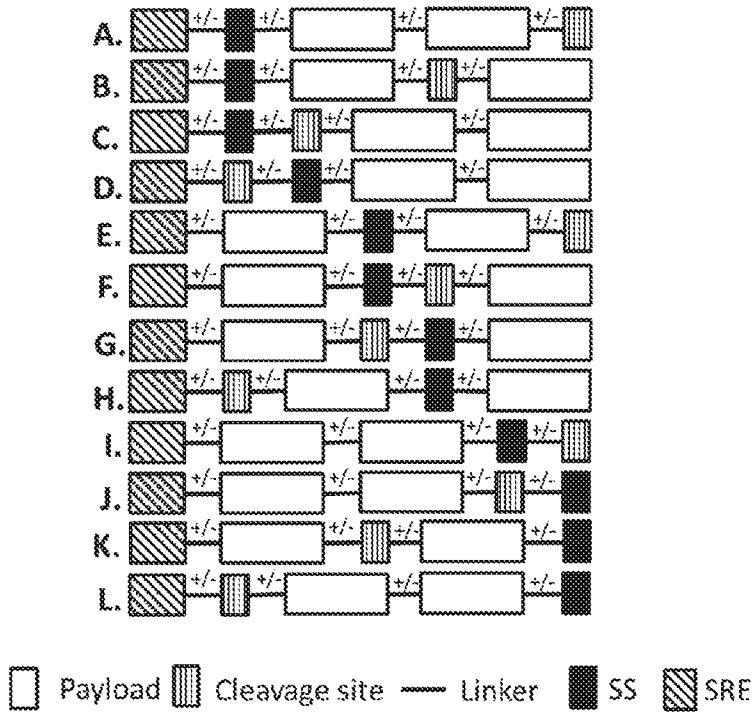

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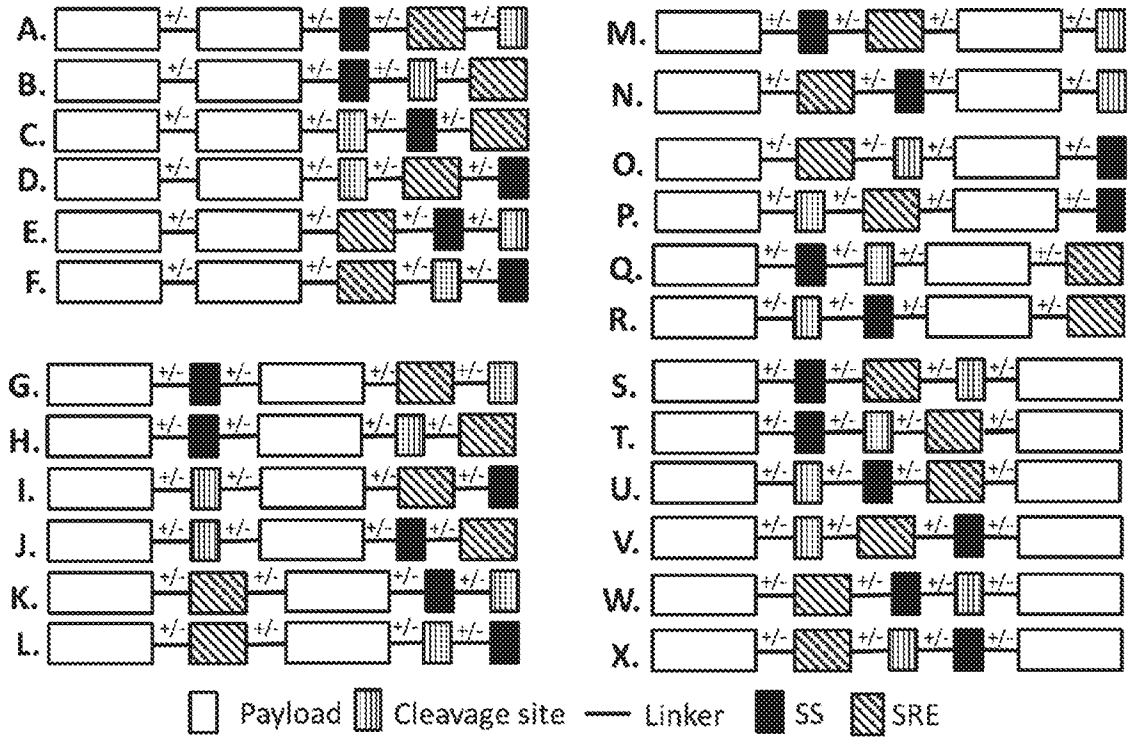

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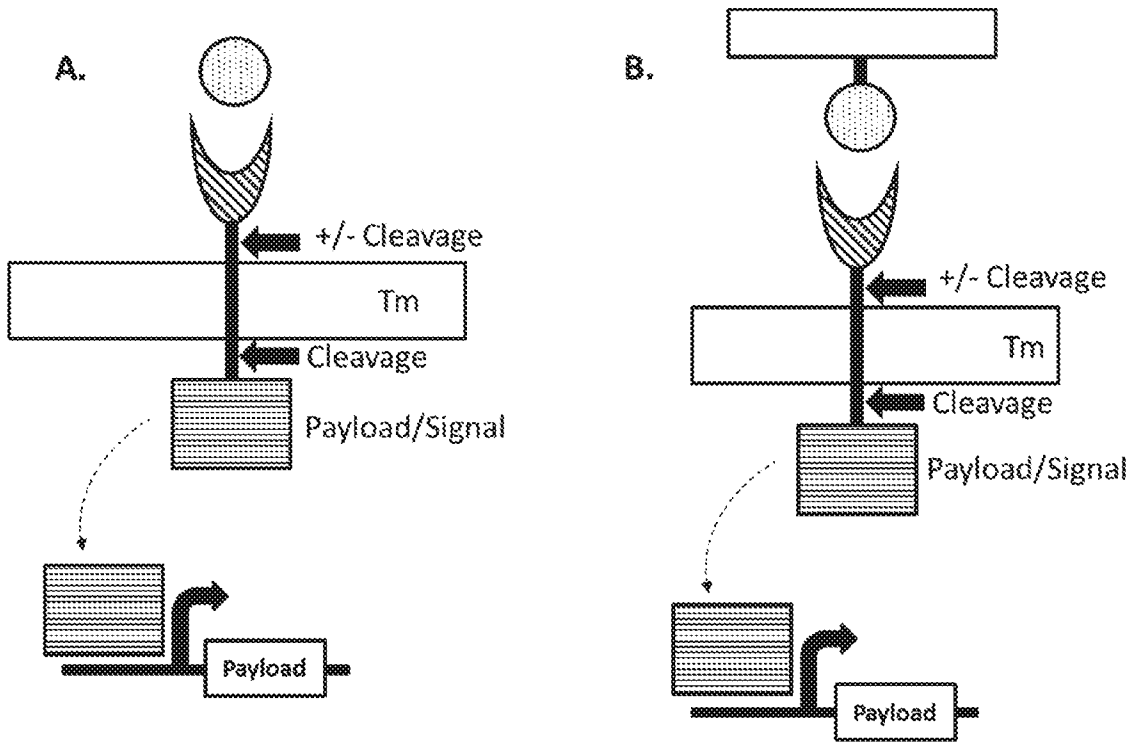

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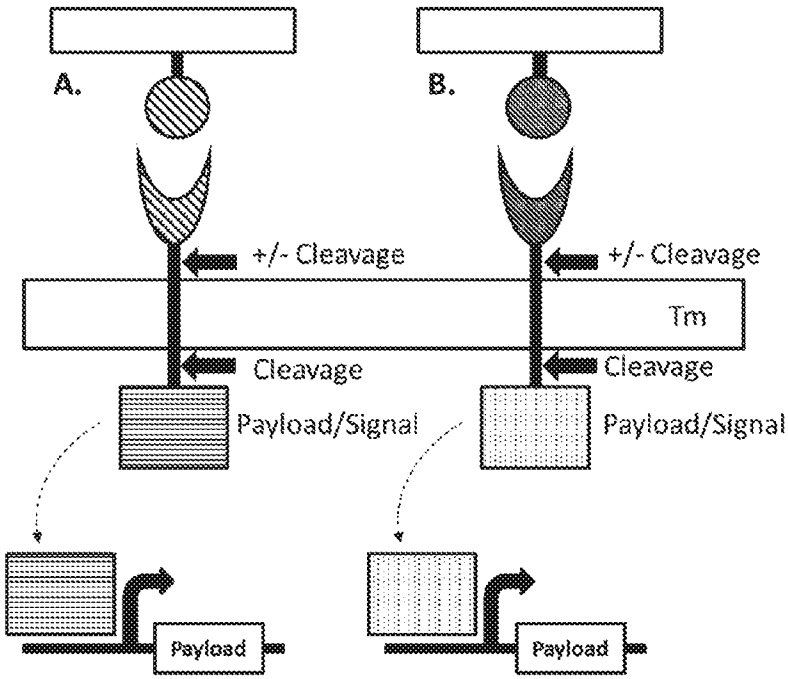
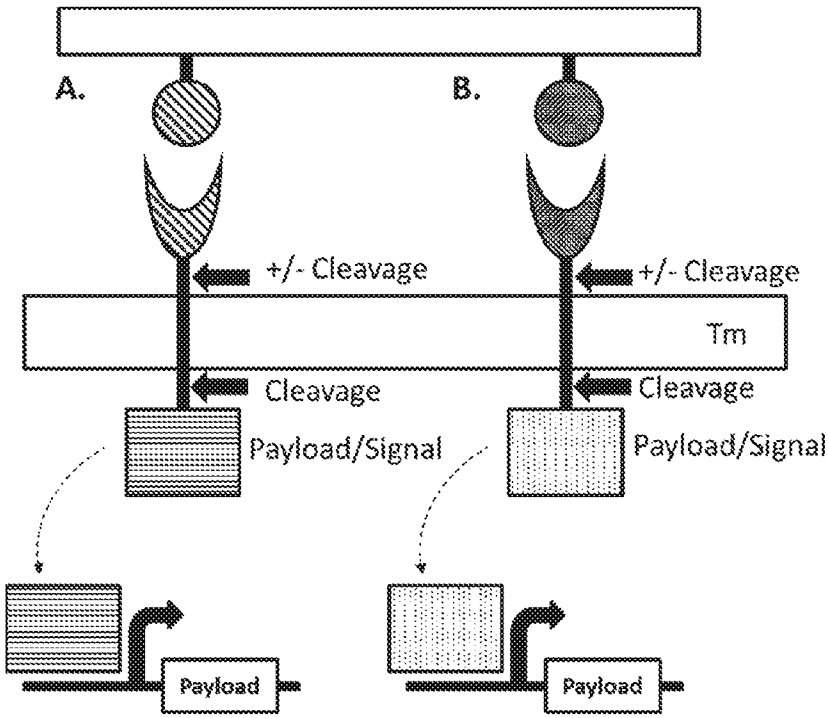


Figure 9



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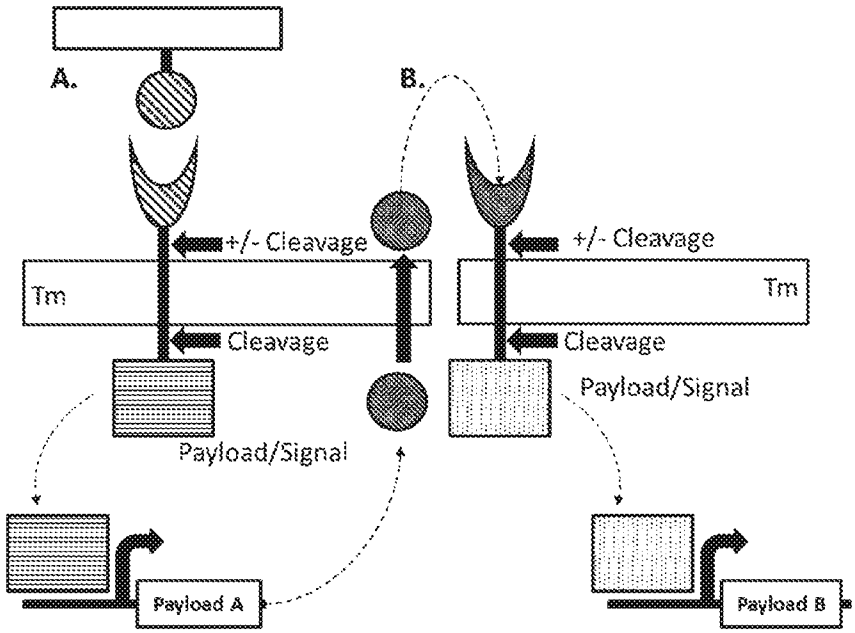

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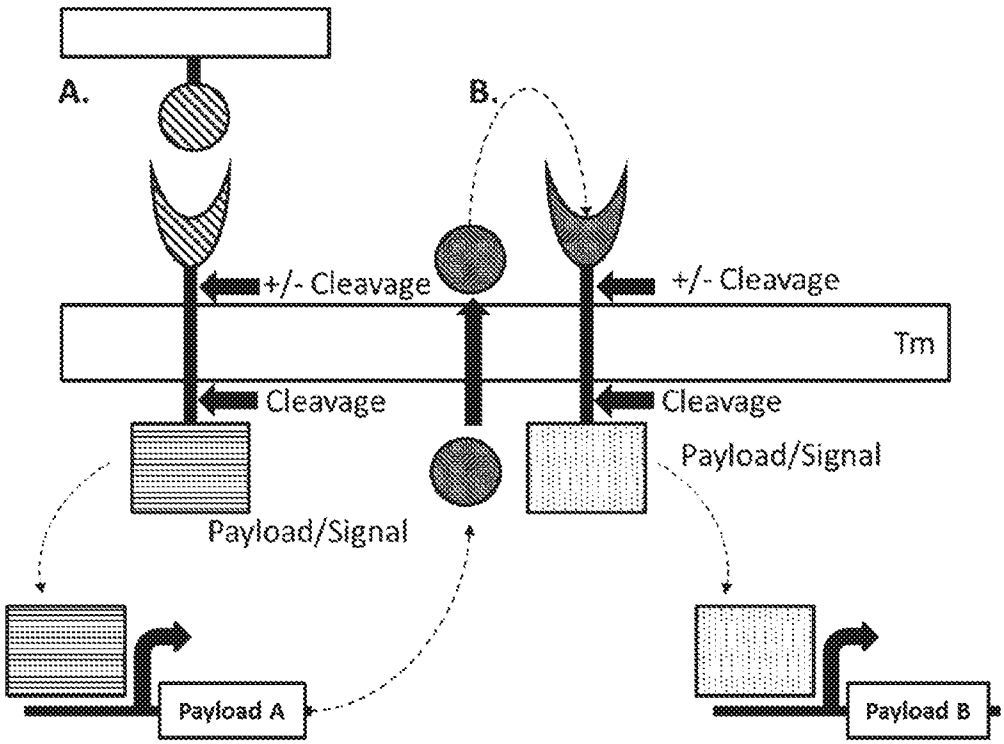
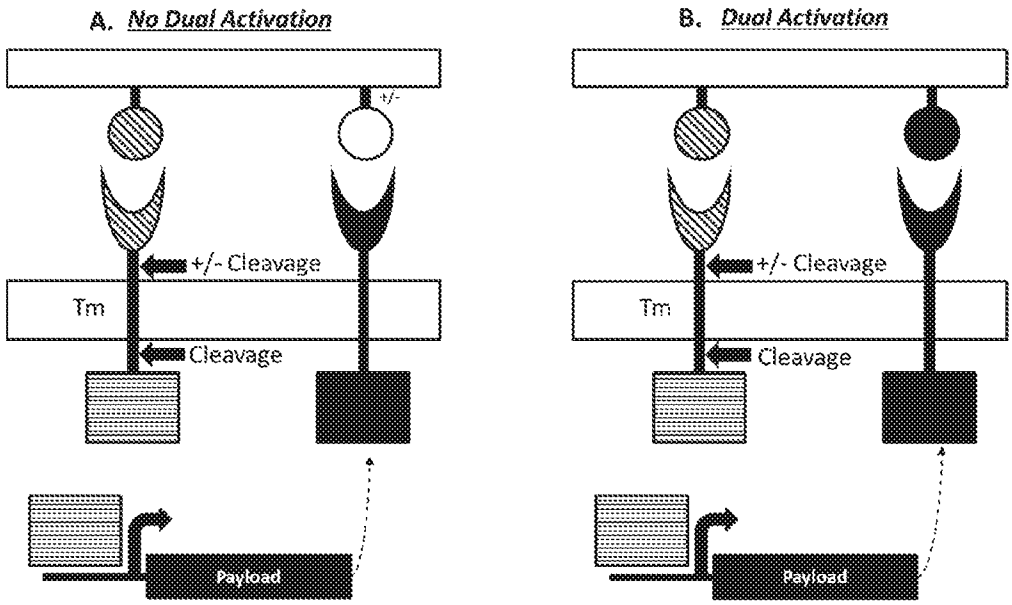


Figure 12



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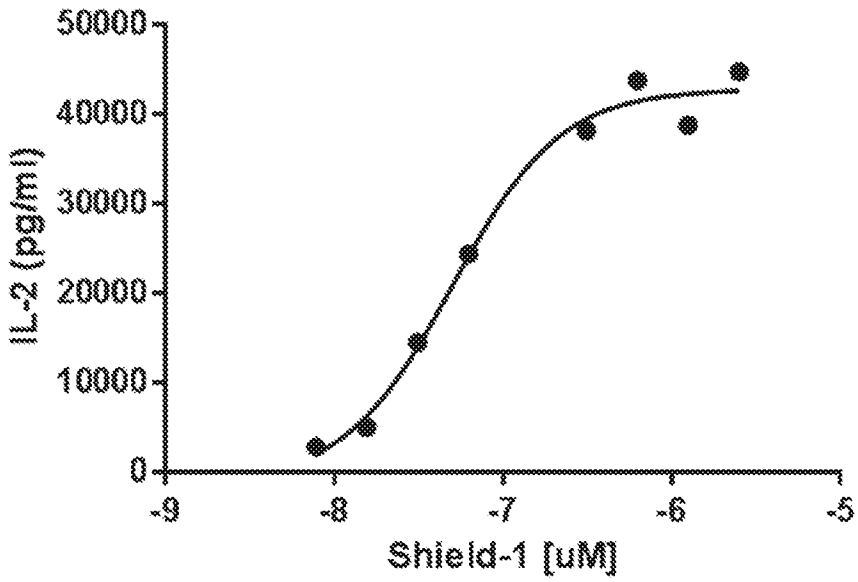


Figure 14

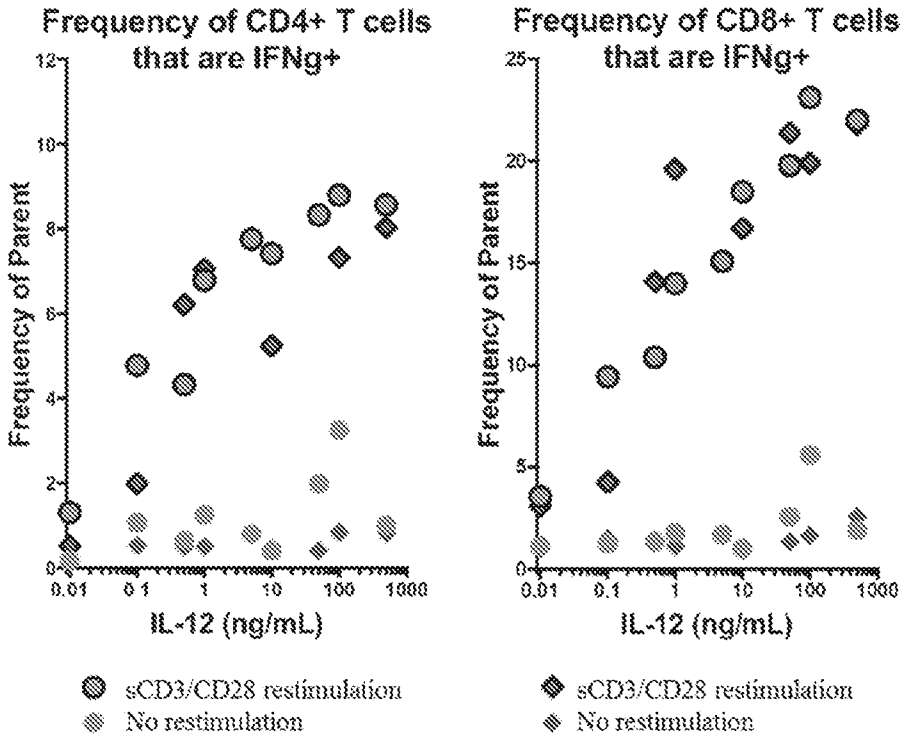
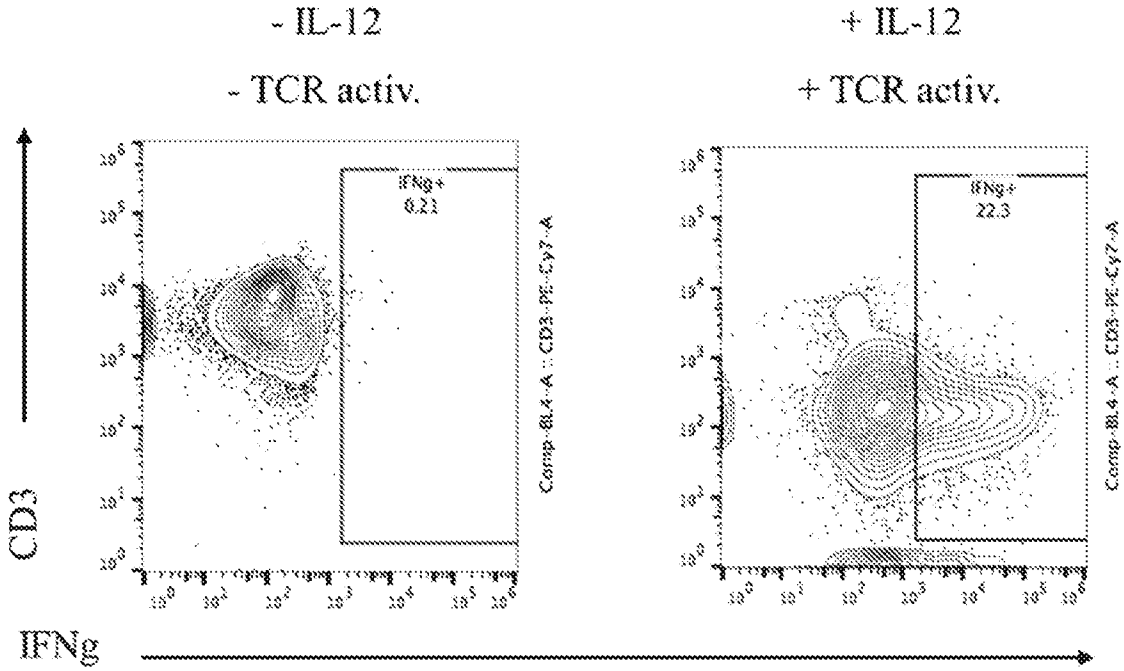


Figure 15A



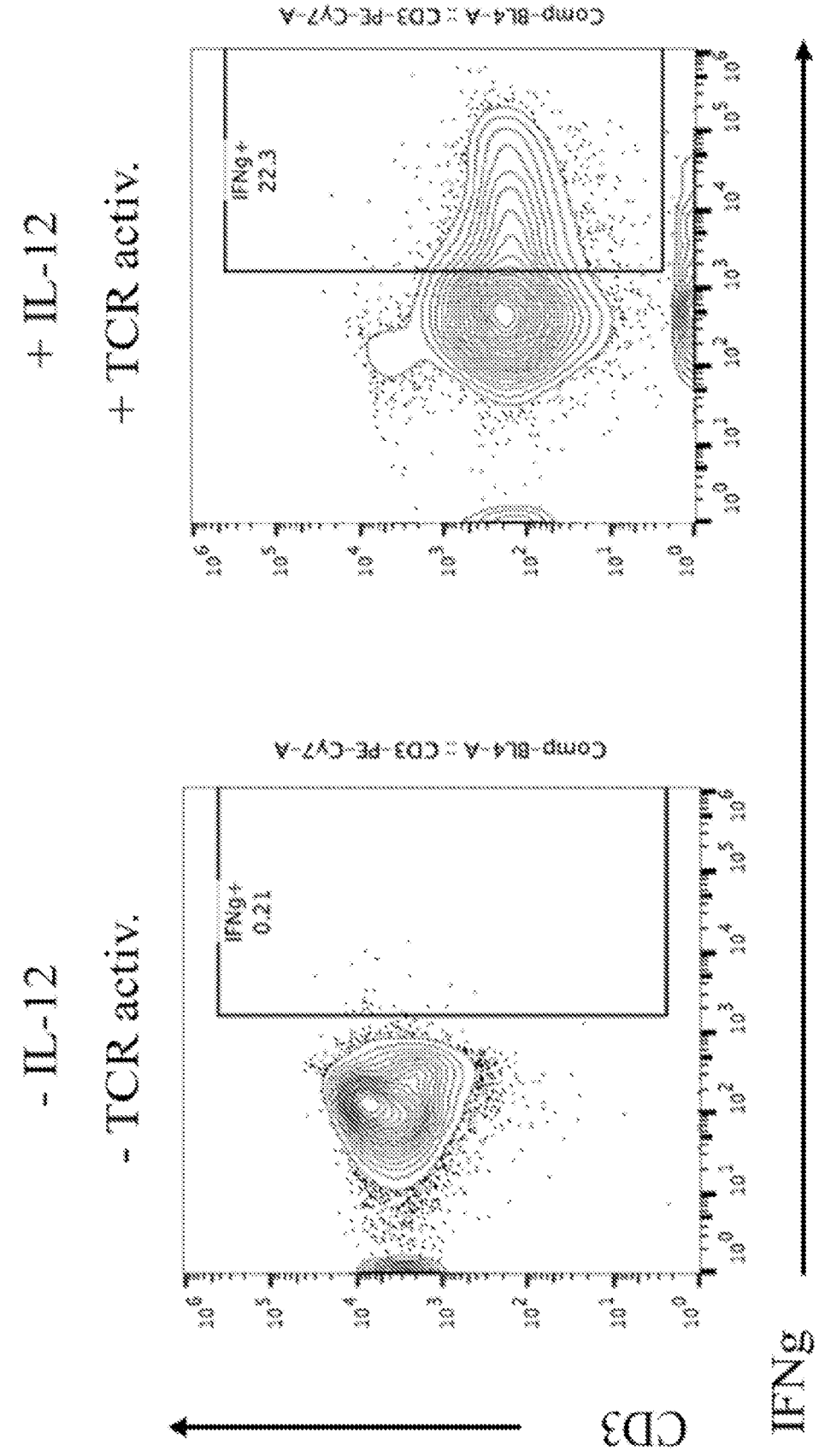
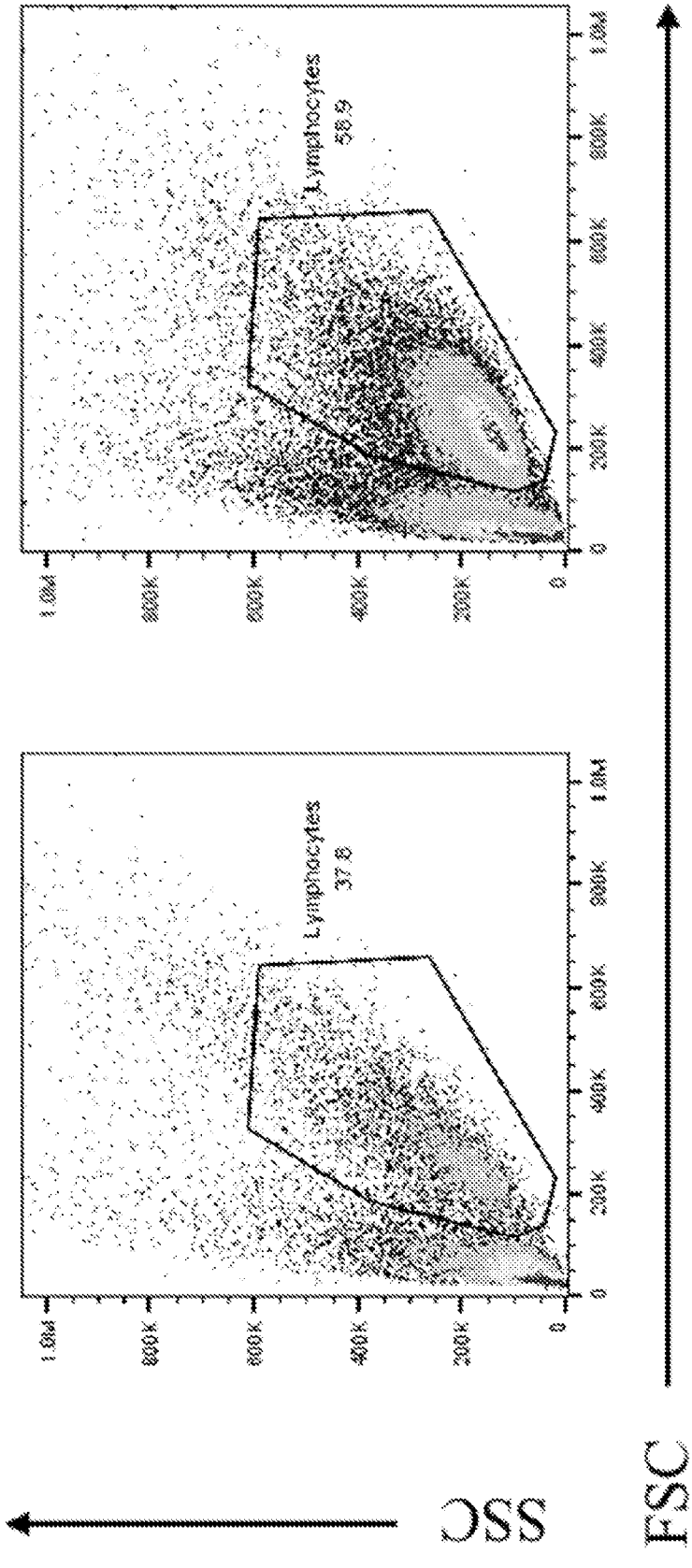

- IL-12
- TCR activ.
+ IL-12
+ TCR activ.
IFNg+
0.21
IFNg+
22.3
Comp-BL4-A :: CD3-PE-Cy7-A
Comp-BL4-A :: CD3-PE-Cy7-A
CD3
IFNg

Figure 15A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+IL-15/IL15Ra
Lymphocytes
37.8
Lymphocytes
38.9
SSC
FSC

Figure 15B

Figure 15C

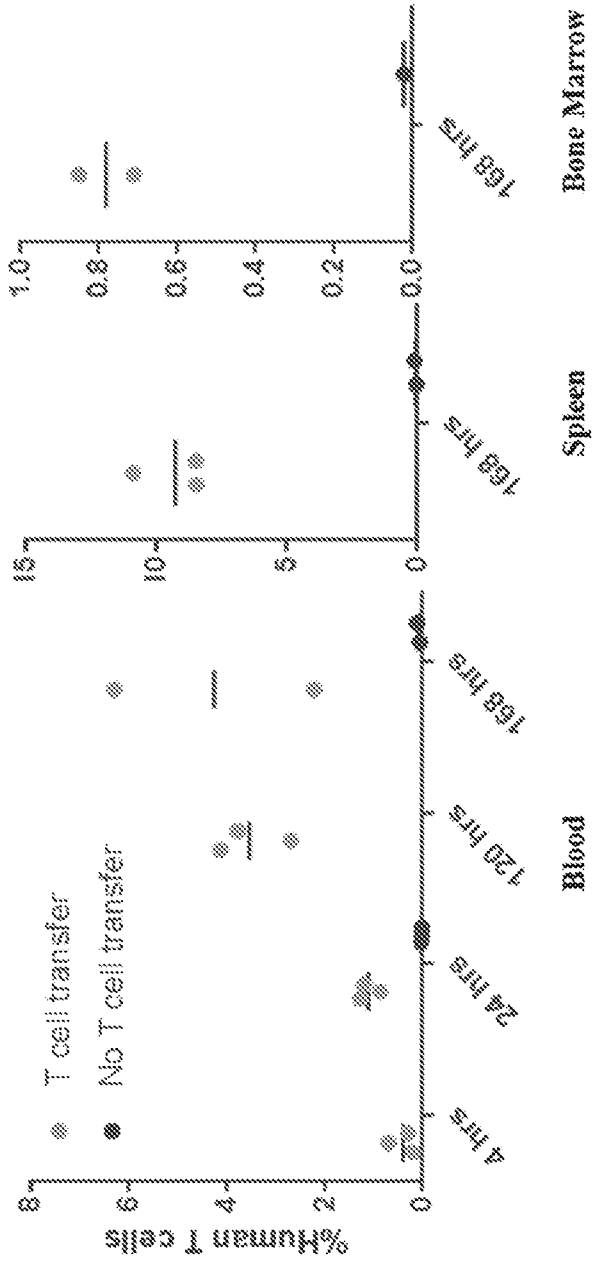
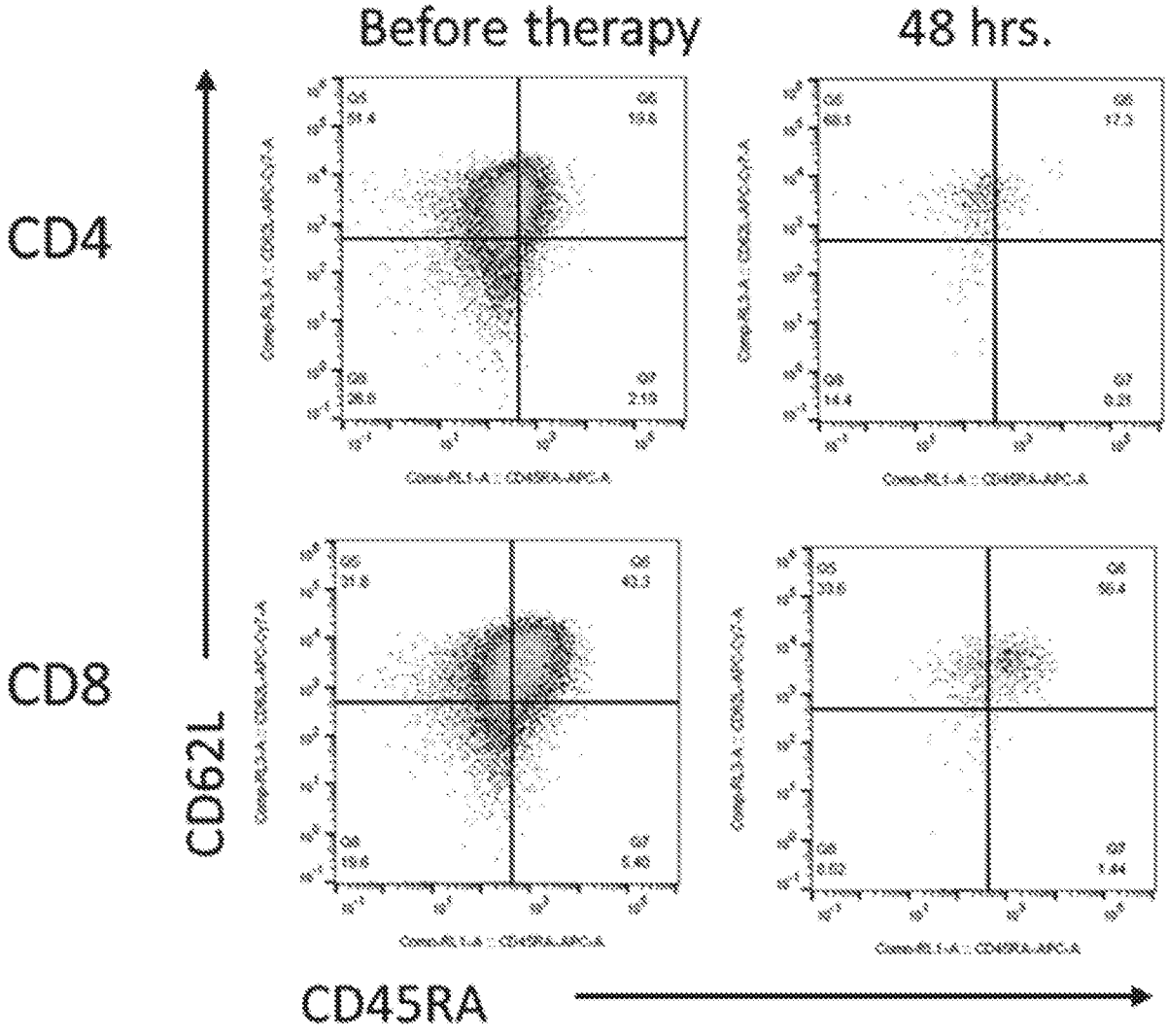

CD3+ CD45+ cells
%Human T cells
T cell transfer
No T cell transfer
Blood
Spleen
Bone Marrow
4 hrs
24 hrs
120 hrs
168 hrs

Figure 15D



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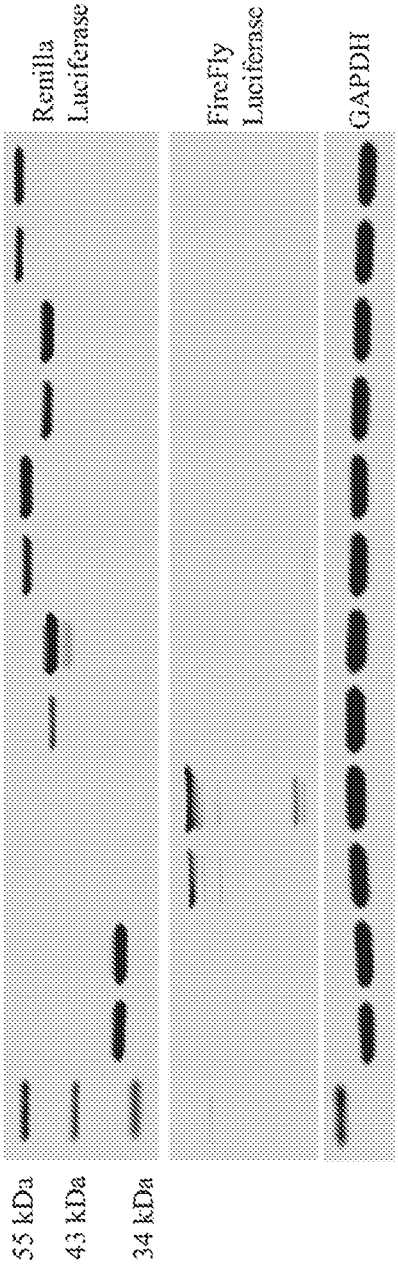
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OT-FLuc-002 Shield-1
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OT-RLuc-004 TMP
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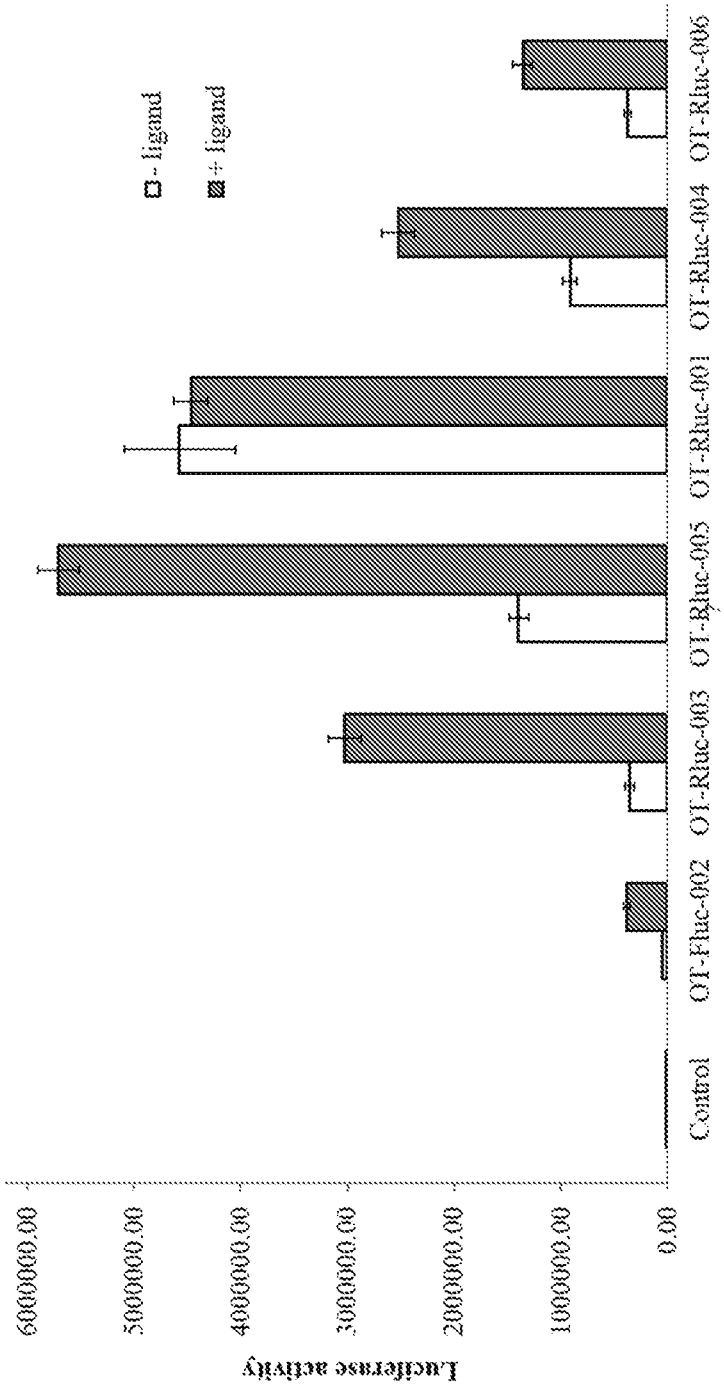
43 kDa
34 kDa
Renilla Luciferase
FireFly Luciferase
GAPDH

Figure 16B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3000000.00
2000000.00
1000000.00
0.00
- ligand
+ ligand
Control
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OT-Rluc-003
OT-Rluc-005
OT-Rluc-001
OT-Rluc-004
OT-Rluc-006

Figure 17A

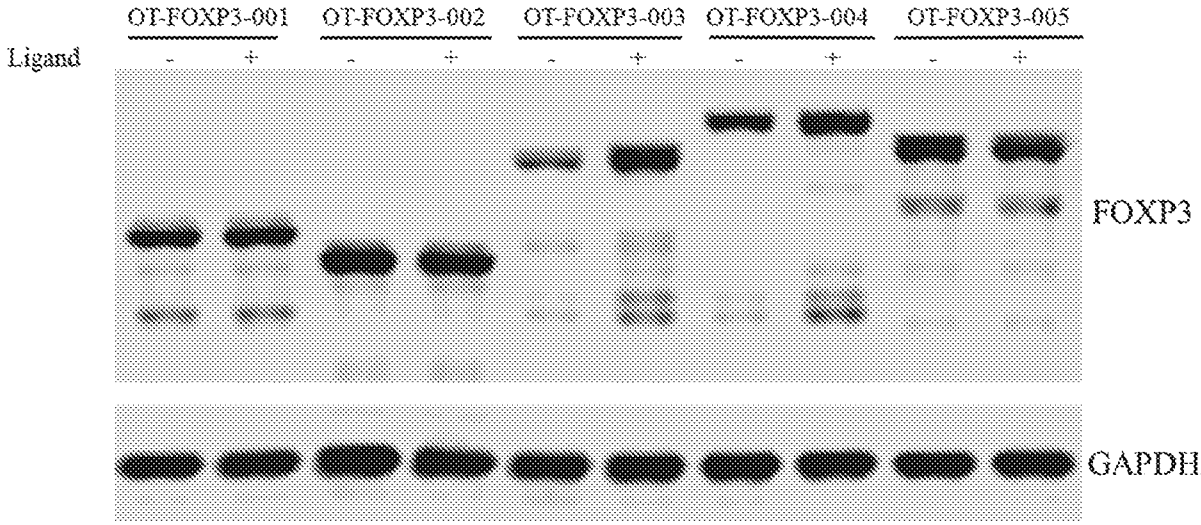
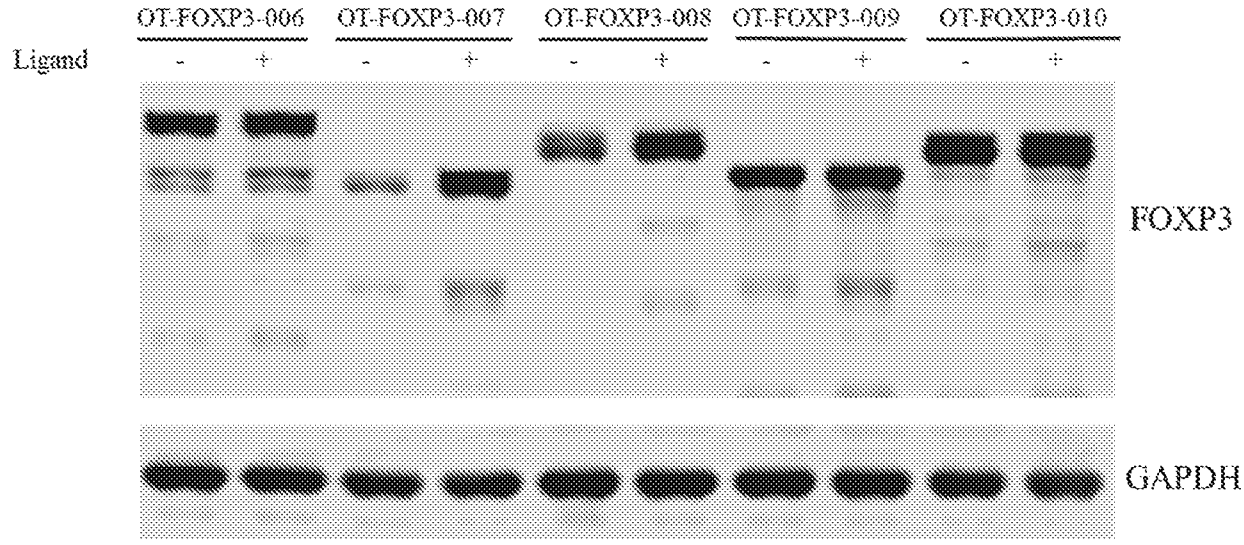


Figure 17B



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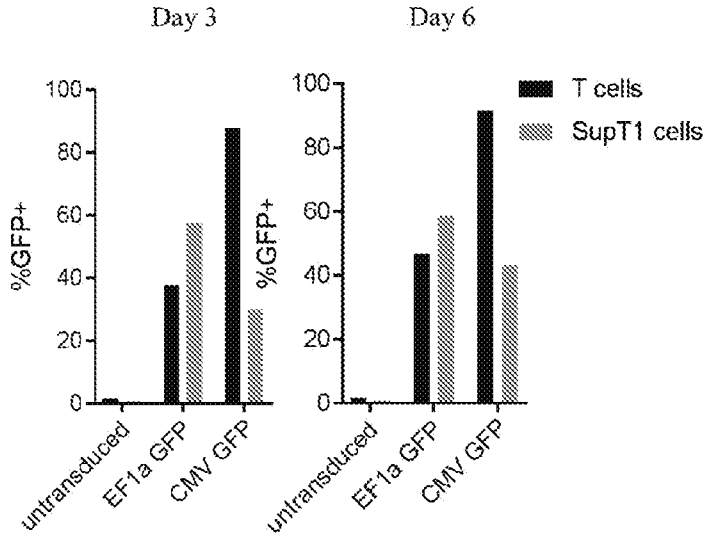

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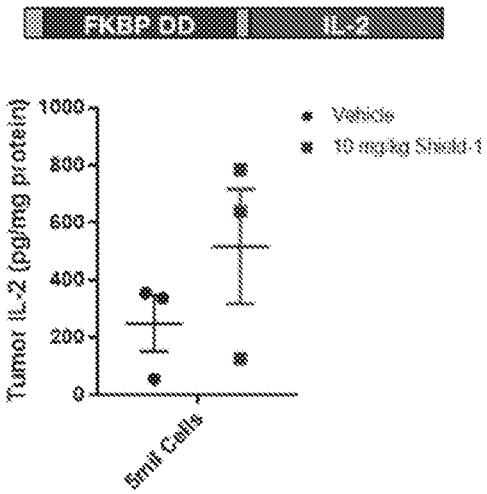

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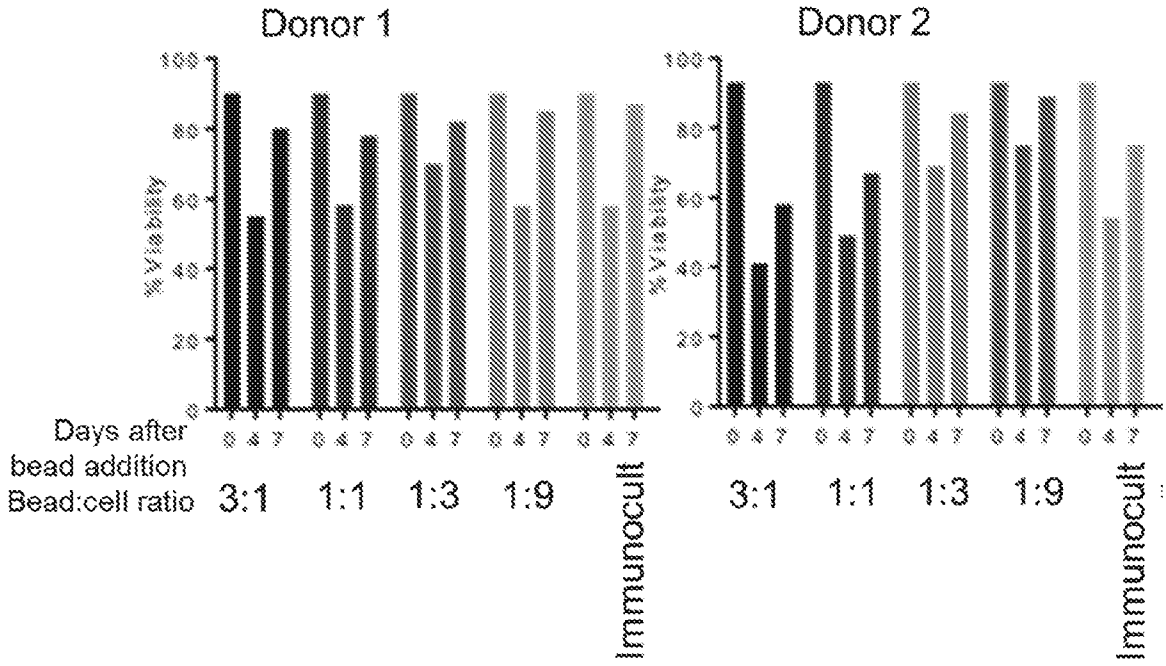

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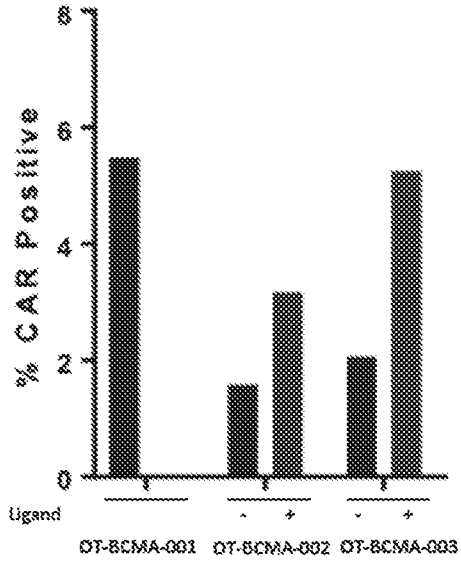

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<120> COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

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

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Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu
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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> 20
<212> PRT
<213> Homo sapiens

<400> 49
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> 50
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Linker sequence

<400> 50
Glu Phe Ser Thr Glu Phe
1   5

<210> 51
<211> 133
<212> PRT
<213> Homo sapiens

<400> 51
Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1   5   10   15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
            20   25   30

Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
        35   40   45

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
    50   55   60

Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
65   70   75   80

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
85 90 95

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
100 105 110

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
115 120 125

Ile Ser Thr Leu Thr
130

<210> 52
<211> 268
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 52
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 Gly Val Gln Val Glu Thr
20 25 30

Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys
35 40 45

Val Val His Tyr Thr Gly Met Leu Glu Asp Gly Lys Lys Val Asp Ser
50 55 60

Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu
65 70 75 80

Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln
85 90 95

```
Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly
            100                 105                 110

His Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu
        115                 120                 125

Leu Leu Lys Pro Glu Met His Ala Pro Thr Ser Ser Ser Thr Lys Lys
    130                 135                 140

Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
145                 150                 155                 160

Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
                165                 170                 175

Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
            180                 185                 190

Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala
        195                 200                 205

Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile
    210                 215                 220

Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
225                 230                 235                 240

Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
                245                 250                 255

Ile Thr Phe Cys Gln Ser Ile Ile Ser Thr Leu Thr
            260                 265
```

<210> 53
<211> 153
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 53
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145 150

<210> 54
<211> 319
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 54

```
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 Met His Ala Pro Thr Ser Ser Ser
            180                 185                 190

Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln
        195                 200                 205
```

Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg
210 215 220

Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys
225 230 235 240

His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu
245 250 255

Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile
260 265 270

Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr
275 280 285

Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu
290 295 300

Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile Ile Ser Thr Leu Thr
305 310 315

<210> 55
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 55
atgtaccgaa tgcaactgct gagctgcatc gccctgagcc tggcactcgt gaccaacagc 60

<210> 56
<211> 60
<212> DNA
<213> Homo sapiens

<400> 56
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60

<210> 57
<211> 18

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 57
gagttcagca ccgagttt 18

<210> 58
<211> 402
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 58
gcgccaacta gtagcagcac aaaaaagaca cagcttcaac tggagcacct gctgctggac 60

ctgcagatga tccttaacgg aatcaacaac tacaagaacc ccaagctgac caggatgctg 120

acgtttaagt tttacatgcc caagaaggcc accgaactca aacacctgca atgcctggag 180

gaagagctga aaccgcttga ggaagtgttg aacctggccc aaagcaagaa tttccacctg 240

aggcccaggg acctgataag caacatcaac gtgatcgtgc tggaactgaa gggtagcgag 300

accaccttca tgtgcgagta cgccgacgag accgcaacca tcgtggagtt cctgaaccga 360

tggataacat tctgccagag catcattagc actctgacct ga 402

<210> 59
<211> 402
<212> DNA
<213> Homo sapiens

<400> 59
gcacctactt caagttctac aaagaaaaca cagctacaac tggagcattt actgctggat 60

ttacagatga ttttgaatgg aattaataat tacaagaatc ccaaactcac caggatgctc 120

acatttaagt tttacatgcc caagaaggcc acagaactga aacatcttca gtgtctagaa 180

gaagaactca aacctctgga ggaagtgcta aatttagctc aaagcaaaaa ctttcactta 240

agacccaggg acttaatcag caatatcaac gtaatagttc tggaactaaa gggatctgaa 300

acaacattca tgtgtgaata tgctgatgag acagcaacca ttgtagaatt tctgaacaga 360

tggattacct tttgtcaaag catcatctca acactgactt ga 402

<210> 60
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilized Domain (DD)

<400> 60
ggcgtgcagg ttgagactat aagcccaggc gacggcagga ccttccccaa gaggggccag 60

acatgcgtgg tgcactacac cggcatgctt gaagacggca aaaaggtgga ctcaagcagg 120

gacaggaaca agcccttcaa gttcatgttg ggcaaacagg aggtgatcag aggctgggag 180

gagggtgttg cccagatgag cgtggggcag agggccaagc tcacgataag tcccgattac 240

gcctacggcg ccaccggtca ccccggcatc atccccccac acgccaccct ggtgttcgac 300

gtggaattgc tgaagcccga g 321

<210> 61
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilized Domain (DD)

<400> 61
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> 62
<211> 807
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 62
atgtaccgaa tgcaactgct gagctgcatc gccctgagcc tggcactcgt gaccaacagc 60

gagttcagca ccgagtttgg cgtgcaggtt gagactataa gcccaggcga cggcaggacc 120

ttccccaaga ggggccagac atgcgtggtg cactacaccg gcatgcttga agacggcaaa 180

aaggtggact caagcaggga caggaacaag cccttcaagt tcatgttggg caaacaggag 240

gtgatcagag gctgggagga gggtgttgcc cagatgagcg tggggcagag ggccaagctc 300

acgataagtc ccgattacgc ctacggcgcc accggtcacc ccggcatcat ccccccacac 360

gccaccctgg tgttcgacgt ggaattgctg aagcccgaga tgcacgcgcc aactagtagc 420

agcacaaaaa agacacagct tcaactggag cacctgctgc tggacctgca gatgatcctt 480

aacggaatca acaactacaa gaaccccaag ctgaccagga tgctgacgtt taagttttac 540

atgcccaaga aggccaccga actcaaacac ctgcaatgcc tggaggaaga gctgaaaccg 600

cttgaggaag tgttgaacct ggcccaaagc aagaatttcc acctgaggcc cagggacctg 660

ataagcaaca tcaacgtgat cgtgctggaa ctgaagggta gcgagaccac cttcatgtgc 720

gagtacgccg acgagaccgc aaccatcgtg gagttcctga accgatggat aacattctgc 780

cagagcatca ttagcactct gacctga 807

<210> 63
<211> 462
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 63

atgtaccgaa tgcaactgct gagctgcatc gccctgagcc tggcactcgt gaccaacagc 60

gcgccaacta gtagcagcac aaaaaagaca cagcttcaac tggagcacct gctgctggac 120

ctgcagatga tccttaacgg aatcaacaac tacaagaacc ccaagctgac caggatgctg 180

acgtttaagt tttacatgcc caagaaggcc accgaactca aacacctgca atgcctggag 240

gaagagctga aaccgcttga ggaagtgttg aacctggccc aaagcaagaa tttccacctg 300

aggcccaggg acctgataag caacatcaac gtgatcgtgc tggaactgaa gggtagcgag 360

accaccttca tgtgcgagta cgccgacgag accgcaacca tcgtggagtt cctgaaccga 420

tggataacat tctgccagag catcattagc actctgacct ga 462

<210> 64
<211> 960
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 64
atgtaccgaa tgcaactgct gagctgcatc gccctgagcc tggcactcgt gaccaacagc 60

gagttcagca ccgagtttat ctctctgatt gcggcgctgg cagttgacta cgttattggc 120

atggaaaacg cgatgccatg gaacctcccg gctgacctgg cgtggttcaa acgtaacacc 180

ctgaacaaac ctgtgatcat gggtcgtcac acctgggaat ctattggccg tcctctcccg 240

ggtcgtaaaa acatcattct gtcttctcag ccaggcaccg acgaccgtgt tacctgggtt 300

aaaagcgttg acgaagcgat tgctgcgtgc ggtgatgttc ctgaaattat ggtgatcggc 360

ggtggccgtg ttatcgaaca gttcctgccg aaagcgcaga aactgtacct gacccacatc 420

gacgcggaag ttgaaggtga cacccacttc ccggactacg aaccggatga ttgggagagc 480

gtattctccg aattccatga tgcggatgcg caaaactctc attcttactg ttttgaaatc 540

ctggaacgtc gtatgcacgc gccaactagt agcagcacaa aaaagacaca gcttcaactg 600

gagcacctgc tgctggacct gcagatgatc cttaacggaa tcaacaacta caagaacccc 660

aagctgacca ggatgctgac gtttaagttt tacatgccca agaaggccac cgaactcaaa 720

cacctgcaat gcctggagga agagctgaaa ccgcttgagg aagtgttgaa cctggcccaa 780

agcaagaatt tccacctgag gcccagggac ctgataagca acatcaacgt gatcgtgctg 840

gaactgaagg gtagcgagac caccttcatg tgcgagtacg ccgacgagac cgcaaccatc 900

gtggagttcc tgaaccgatg gataacattc tgccagagca tcattagcac tctgacctga 960

<210> 65
<211> 415
<212> PRT
<213> Homo sapiens

<400> 65
Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu Val
1 5 10 15

Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg Glu
20 25 30

Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser Gly
35 40 45

Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr Arg
50 55 60

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

Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg Gln Ala Ala Lys
85 90 95

Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg Pro
100 105 110

Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro Val
115 120 125

Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser Leu
130 135 140

Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys Gly
145 150 155 160

```
His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly Leu
                165                 170                 175

Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg Arg
            180                 185                 190

Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr Ala
        195                 200                 205

Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His Gly
    210                 215                 220

Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln Ala
225                 230                 235                 240

Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys Pro
                245                 250                 255

Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys Pro
            260                 265                 270

Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly Gly
        275                 280                 285

Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu Asp
    290                 295                 300

Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln Glu
305                 310                 315                 320

Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro Thr
                325                 330                 335

Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val Ser
            340                 345                 350

Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp Asp
        355                 360                 365
```

```
Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu Leu
    370                 375                 380

Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met Pro
385                 390                 395                 400

Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
                405                 410                 415
```

<210> 66
<211> 285
<212> PRT
<213> Homo sapiens

<400> 66

```
Gly Val Asp Gly Phe Gly Asp Val Gly Ala Leu Glu Ser Leu Arg Gly
1               5                   10                  15

Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys Gly His Cys
            20                  25                  30

Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly Leu Arg Thr
        35                  40                  45

Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg Arg Phe Ser
    50                  55                  60

Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr Ala Lys Lys
65                  70                  75                  80

Met Val Leu Ala Leu Leu Glu Leu Ala Arg Gln Asp His Gly Ala Leu
                85                  90                  95

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

Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys Pro Val Ser
        115                 120                 125
```

```
Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys Pro Ser Leu
    130                 135                 140

Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly Gly Glu Gln
145                 150                 155                 160

Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu Asp Glu Ser
                165                 170                 175

Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln Glu Gly Leu
            180                 185                 190

Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro Thr Pro Ser
        195                 200                 205

Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val Ser Trp Arg
    210                 215                 220

Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp Asp Ile Phe
225                 230                 235                 240

Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu Leu Arg Val
                245                 250                 255

Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met Pro Gly Cys
            260                 265                 270

Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
        275                 280                 285
```

<210> 67
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 67

```
Val Asp Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Leu Asp
1               5                   10
```

<210> 68
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 68
Ser Gly Gly Gly Ser
1 5

<210> 69
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 69
agcggcggtg gcagc 15

<210> 70
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 70
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 Leu Glu
100 105

<210> 71
<211> 158
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 71
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 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> 72
<211> 528
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Payload sequence

<400> 72
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 Ser Gly Gly Gly
            100   105   110

Ser Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu

```
        115                 120                 125

Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg
    130                 135                 140

Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser
145                 150                 155                 160

Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr
                165                 170                 175

Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr
            180                 185                 190

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

Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg
    210                 215                 220

Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro
225                 230                 235                 240

Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
                245                 250                 255

Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
            260                 265                 270

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
        275                 280                 285

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
    290                 295                 300

Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
305                 310                 315                 320

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His
```

325 330 335

Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
340 345 350

Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
355 360 365

Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys
370 375 380

Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
385 390 395 400

Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
405 410 415

Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
420 425 430

Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
435 440 445

Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
450 455 460

Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
465 470 475 480

Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
485 490 495

Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
500 505 510

Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
515 520 525

<210> 73

<211> 579
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 73

```
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 Ser
145                 150                 155                 160

Gly Gly Gly Ser Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg
                165                 170                 175
```

```
Leu Arg Leu Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu
            180                 185                 190

Leu Ser Arg Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg
        195                 200                 205

Ala Gly Ser Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp
    210                 215                 220

Leu Glu Thr Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu
225                 230                 235                 240

Glu Asp Thr Gly Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg
                245                 250                 255

Gln Ala Ala Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val
            260                 265                 270

Val Leu Arg Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr
        275                 280                 285

Pro Arg Pro Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala
    290                 295                 300

Leu Glu Ser Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met
305                 310                 315                 320

Glu Pro Cys Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg
                325                 330                 335

Glu Ser Gly Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys
            340                 345                 350

Leu Arg Arg Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly
        355                 360                 365

Asp Leu Thr Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln
    370                 375                 380
```

```
Gln Asp His Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His
385                 390                 395                 400

Gly Cys Gln Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr
                405                 410                 415

Asp Gly Cys Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly
            420                 425                 430

Thr Ser Cys Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln
        435                 440                 445

Ala Cys Gly Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr
    450                 455                 460

Ser Pro Glu Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr
465                 470                 475                 480

Pro Phe Gln Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser
                485                 490                 495

Ser Leu Pro Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro
            500                 505                 510

Gly Phe Val Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu
        515                 520                 525

Thr Leu Asp Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln
    530                 535                 540

Ser Leu Leu Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr
545                 550                 555                 560

Lys Gln Met Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe
                565                 570                 575

Lys Thr Ser
```

<210> 74
<211> 607
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 74
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 Ser Gly Gly Gly Ser
            180                 185                 190

Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu Val
        195                 200                 205

Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg Glu
    210                 215                 220

Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser Gly
225                 230                 235                 240

Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr Arg
                245                 250                 255

Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr Gly
            260                 265                 270

Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg Gln Ala Ala Lys
        275                 280                 285

Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg Pro
    290                 295                 300

Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro Val
305                 310                 315                 320

Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser Leu
                325                 330                 335

Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys Gly
            340                 345                 350

His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly Leu
        355                 360                 365

Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg Arg
```

```
    370                 375                 380

Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr Ala
385                 390                 395                 400

Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His Gly
                405                 410                 415

Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln Ala
            420                 425                 430

Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys Pro
        435                 440                 445

Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys Pro
    450                 455                 460

Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly Gly
465                 470                 475                 480

Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu Asp
                485                 490                 495

Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln Glu
            500                 505                 510

Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro Thr
        515                 520                 525

Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val Ser
    530                 535                 540

Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp Asp
545                 550                 555                 560

Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu Leu
                565                 570                 575

Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met Pro
```

580 585 590

Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
595 600 605

<210> 75
<211> 607
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 75
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 Ser Gly Gly Gly Ser
            180                 185                 190

Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu Val
        195                 200                 205

Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg Glu
    210                 215                 220

Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser Gly
225                 230                 235                 240

Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr Arg
                245                 250                 255

Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr Gly
            260                 265                 270

Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg Gln Ala Ala Lys
        275                 280                 285

Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg Pro
    290                 295                 300

Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro Val
305                 310                 315                 320

Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser Leu
                325                 330                 335

Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys Gly
            340                 345                 350
```

```
His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly Leu
        355                 360                 365

Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg Arg
    370                 375                 380

Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr Ala
385                 390                 395                 400

Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His Gly
                405                 410                 415

Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln Ala
            420                 425                 430

Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys Pro
        435                 440                 445

Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys Pro
    450                 455                 460

Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly Gly
465                 470                 475                 480

Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu Asp
                485                 490                 495

Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln Glu
            500                 505                 510

Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro Thr
        515                 520                 525

Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val Ser
    530                 535                 540

Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp Asp
545                 550                 555                 560
```

Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu Leu
565 570 575

Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met Pro
580 585 590

Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
595 600 605

<210> 76
<211> 607
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 76
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 Ser Gly Gly Gly Ser
            180                 185                 190

Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu Val
        195                 200                 205

Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg Glu
    210                 215                 220

Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser Gly
225                 230                 235                 240

Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr Arg
                245                 250                 255

Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr Gly
            260                 265                 270

Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg Gln Ala Ala Lys
        275                 280                 285

Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg Pro
    290                 295                 300

Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro Val
305                 310                 315                 320

Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser Leu
```

325 330 335

Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys Gly
340 345 350

His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly Leu
355 360 365

Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg Arg
370 375 380

Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr Ala
385 390 395 400

Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His Gly
405 410 415

Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln Ala
420 425 430

Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys Pro
435 440 445

Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys Pro
450 455 460

Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly Gly
465 470 475 480

Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu Asp
485 490 495

Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln Glu
500 505 510

Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro Thr
515 520 525

Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val Ser

530 535 540

Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp Asp
545 550 555 560

Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu Leu
565 570 575

Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met Pro
580 585 590

Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
595 600 605

<210> 77
<211> 413
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 77
Met Leu Glu Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg
1 5 10 15

Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met
20 25 30

Leu Glu Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro
35 40 45

Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu
50 55 60

Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser
65 70 75 80

Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro
85 90 95

```
His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu Glu Ser Gly
            100                 105                 110

Gly Gly Ser Gly Val Asp Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
        115                 120                 125

Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
    130                 135                 140

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
145                 150                 155                 160

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
                165                 170                 175

Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
            180                 185                 190

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Arg Gln Asp His
        195                 200                 205

Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
    210                 215                 220

Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
225                 230                 235                 240

Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys
                245                 250                 255

Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
            260                 265                 270

Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
        275                 280                 285

Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
    290                 295                 300
```

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Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
305                 310                 315                 320


Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
                325                 330                 335


Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
            340                 345                 350


Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
        355                 360                 365


Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
    370                 375                 380


Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
385                 390                 395                 400


Gln Leu Ile Gly Met Leu Gln Gly Leu Met Arg Asp Leu
                405                 410


<210> 78
<211> 525
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Payload sequence

<400> 78
Met Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu
1               5                   10                  15


Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg
            20                  25                  30


Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser
        35                  40                  45


Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr
```

50 55 60

Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr
65 70 75 80

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

Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg
100 105 110

Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro
115 120 125

Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
130 135 140

Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
145 150 155 160

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
165 170 175

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
180 185 190

Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
195 200 205

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His
210 215 220

Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
225 230 235 240

Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
245 250 255

Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys

```
            260                 265                 270

Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
        275                 280                 285

Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
    290                 295                 300

Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
305                 310                 315                 320

Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
                325                 330                 335

Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
            340                 345                 350

Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
        355                 360                 365

Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
    370                 375                 380

Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
385                 390                 395                 400

Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
                405                 410                 415

Ser Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr
            420                 425                 430

Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu
        435                 440                 445

Gly Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe
    450                 455                 460

Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly
```

465 470 475 480

Val Ala Gln Met Ser Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro
485 490 495

Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His
500 505 510

Ala Thr Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
515 520 525

<210> 79
<211> 576
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 79
Met Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu
1 5 10 15

Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg
20 25 30

Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser
35 40 45

Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr
50 55 60

Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr
65 70 75 80

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

Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg
100 105 110

```
Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro
        115                 120                 125

Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
    130                 135                 140

Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
145                 150                 155                 160

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
                165                 170                 175

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
            180                 185                 190

Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
        195                 200                 205

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His
    210                 215                 220

Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
225                 230                 235                 240

Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
                245                 250                 255

Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys
            260                 265                 270

Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
        275                 280                 285

Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
    290                 295                 300

Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
305                 310                 315                 320
```

```
Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
                325                 330                 335

Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
            340                 345                 350

Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
        355                 360                 365

Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
    370                 375                 380

Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
385                 390                 395                 400

Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
                405                 410                 415

Ser Gly Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly
            420                 425                 430

Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe
        435                 440                 445

Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met Gly Arg His Thr Trp
    450                 455                 460

Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser
465                 470                 475                 480

Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp
                485                 490                 495

Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly
            500                 505                 510

Gly Gly Arg Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr
        515                 520                 525
```

Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp
530 535 540

Tyr Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala
545 550 555 560

Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
565 570 575

<210> 80
<211> 576
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 80
Met Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu
1 5 10 15

Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg
20 25 30

Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser
35 40 45

Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr
50 55 60

Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr
65 70 75 80

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

Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg
100 105 110

Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro

```
        115                 120                 125

Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
    130                 135                 140

Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
145                 150                 155                 160

Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
                165                 170                 175

Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
            180                 185                 190

Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
        195                 200                 205

Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His
    210                 215                 220

Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
225                 230                 235                 240

Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
                245                 250                 255

Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys
            260                 265                 270

Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
        275                 280                 285

Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
    290                 295                 300

Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
305                 310                 315                 320

Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
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325 330 335

Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
340 345 350

Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
355 360 365

Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
370 375 380

Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
385 390 395 400

Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
405 410 415

Ser Gly Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly
420 425 430

Met Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe
435 440 445

Lys Arg Asn Thr Leu Asn Lys Pro Val Ile Met Gly Arg His Thr Trp
450 455 460

Glu Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser
465 470 475 480

Ser Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp
485 490 495

Glu Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly
500 505 510

Gly Gly Arg Val Tyr Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr
515 520 525

Leu Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp

530 535 540

Tyr Lys Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala
545 550 555 560

Asp Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
565 570 575

<210> 81
<211> 1245
<212> DNA
<213> Homo sapiens

<400> 81
gacgaagcgg atcggcggct cctgcggcgg tgccggctgc ggctggtgga agagctgcag 60

gtggaccagc tctgggacgc cctgctgagc cgcgagctgt tcaggcccca tatgatcgag 120

gacatccagc gggcaggctc tggatctcgg cgggatcagg ccaggcagct gatcatagat 180

ctggagactc gagggagtca ggctcttcct ttgttcatct cctgcttaga ggacacaggc 240

caggacatgc tggcttcgtt tctgcgaact aacaggcaag cagcaaagtt gtcgaagcca 300

accctagaaa accttacccc agtggtgctc agaccagaga ttcgcaaacc agaggttctc 360

agaccggaaa cacccagacc agtggacatt ggttctggag gatttggtga tgtcggtgct 420

cttgagagtt tgaggggaaa tgcagatttg gcttacatcc tgagcatgga gccctgtggc 480

cactgcctca ttatcaacaa tgtgaacttc tgccgtgagt ccgggctccg cacccgcact 540

ggctccaaca tcgactgtga gaagttgcgg cgtcgcttct cctcgctgca tttcatggtg 600

gaggtgaagg gcgacctgac tgccaagaaa atggtgctgg ctttgctgga gctggcgcag 660

caggaccacg gtgctctgga ctgctgcgtg gtggtcattc tctctcacgg ctgtcaggcc 720

agccacctgc agttcccagg ggctgtctac ggcacagatg gatgccctgt gtcggtcgag 780

aagattgtga acatcttcaa tgggaccagc tgccccagcc tgggagggaa gcccaagctc 840

tttttcatcc aggcctgtgg tggggagcag aaagaccatg ggtttgaggt ggcctccact 900

tcccctgaag acgagtcccc tggcagtaac cccgagccag atgccacccc gttccaggaa 960

ggtttgagga ccttcgacca gctggacgcc atatctagtt tgcccacacc cagtgacatc 1020

tttgtgtcct actctacttt cccaggtttt gtttcctgga gggaccccaa gagtggctcc 1080

tggtacgttg agaccctgga cgacatcttt gagcagtggg ctcactctga agacctgcag 1140

tccctcctgc ttagggtcgc taatgctgtt tcggtgaaag ggatttataa acagatgcct 1200

ggttgcttta atttcctccg gaaaaaactt ttctttaaaa catca 1245

<210> 82
<211> 1245
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 82
gacgaggccg acagaaggct tttgagaagg tgcaggctcc ggctggttga ggagctgcaa 60

gtcgaccaac tgtgggacgc cctgctgtcc agggaactgt ttaggcccca catgatcgag 120

gacatccaaa gagccgggtc aggatctagg agggatcagg ctaggcaact tattatcgat 180

ctggaaacca gggggagcca agcccttccc ctcttcatca gctgtctcga ggatacgggc 240

caagacatgc tcgccagttt tctgagaacg aaccgacagg ccgcaaagct gagtaaaccc 300

accctggaga accttacccc tgtggtactc aggcccgaaa tccggaagcc cgaggtgctg 360

aggccggaga ctccgaggcc cgtggacatc ggcagtgggg ggttcggtga cgtgggagcg 420

ctggaaagcc tgcgcggcaa cgctgacctc gcctacatcc ttagcatgga gccgtgcgga 480

cactgtctga tcatcaacaa cgtgaacttc tgcagggaga gcgggctgcg gaccaggacc 540

gggagcaata tcgattgcga aaaactgagg aggaggttca gctcactgca cttcatggtg 600

gaggtgaagg gcgacctgac cgccaagaag atggttctgg ccttgcttga gcttgcgcag 660

caagatcacg gtgcccttga ctgttgtgtg gtggtgatac tgagccacgg ctgtcaggcc 720

agccacctgc agtttccggg tgctgtctac gggaccgacg ggtgccccgt gtctgtcgaa 780

aagatagtga acatcttcaa cggcacgtcc tgcccctcac tgggcggcaa gcccaagctc 840

ttctttatac aggcttgcgg tggagagcag aaggaccatg gcttcgaggt ggccagcacc 900

agccccgagg acgagagccc tggtagcaat cccgagcccg atgccacccc atttcaagaa 960

ggattgagga ccttcgatca gctcgacgcg attagctctc tgcccacccc cagcgacatt 1020

tttgtgagct acagcacgtt cccgggtttc gtcagttgga gggaccctaa gagcggaagc 1080

tggtatgtgg agacgctgga cgacatattc gagcaatggg cacacagcga ggatctgcag 1140

tcactcctgt tgcgcgtggc caacgccgtt tccgttaagg gcatctataa gcagatgcca 1200

ggttgtttca atttcctccg aaaaaagttg ttctttaaga ccagc 1245

<210> 83
<211> 855
<212> DNA
<213> Homo sapiens

<400> 83
ggcgtggacg ggttcggtga cgtgggagcg ctggaaagcc tgcgcggcaa cgctgacctc 60

gcctacatcc ttagcatgga gccgtgcgga cactgtctga tcatcaacaa cgtgaacttc 120

tgcagggaga gcgggctgcg gaccaggacc gggagcaata tcgattgcga aaaactgagg 180

aggaggttca gctcactgca cttcatggtg gaggtgaagg gcgacctgac cgccaagaag 240

atggttctgg ccttgcttga gcttgcgcgg caagatcacg gtgcccttga ctgttgtgtg 300

gtggtgatac tgagccacgg ctgtcaggcc agccacctgc agtttccggg tgctgtctac 360

gggaccgacg ggtgccccgt gtctgtcgaa aagatagtga acatcttcaa cggcacgtcc 420

tgcccctcac tgggcggcaa gcccaagctc ttctttatac aggcttgcgg tggagagcag 480

aaggaccatg gcttcgaggt ggccagcacc agccccgagg acgagagccc tggtagcaat 540

cccgagcccg atgccacccc atttcaagaa ggattgagga ccttcgatca gctcgacgcg 600

attagctctc tgcccacccc cagcgacatt tttgtgagct acagcacgtt cccgggtttc 660

gtcagttgga gggaccctaa gagcggaagc tggtatgtgg agacgctgga cgacatattc 720

gagcaatggg cacacagcga ggatctgcag tcactcctgt tgcgcgtggc caacgccgtt 780

tccgttaagg gcatctataa gcagatgcca ggttgtttca atttcctccg aaaaaagttg 840

ttctttaaga ccagc 855

<210> 84
<211> 39
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 84
gtcgactatc cctacgatgt tccggactac gcactggac 39

<210> 85
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 85
tcaggtggcg gtagt 15

<210> 86
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 86
tcaggcgggg ggagt 15

<210> 87
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 87
ggcgtgcagg ttgagactat aagcccaggc gacggcagga ccttccccaa gaggggccag 60

acatgcgtgg tgcactacac cggcatgctt gaagacggca aaaaggtgga ctcaagcagg 120

gacaggaaca agcccttcaa gttcatgttg ggcaaacagg aggtgatcag aggctgggag 180

gagggtgttg cccagatgag cgtggggcag agggccaagc tcacgataag tcccgattac 240

gcctacggcg ccaccggtca ccccggcatc atccccccac acgccaccct ggtgttcgac 300

gtggaattgc tgaagctgga g 321

<210> 88
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 88
ggcgtgcagg ttgagactat aagcccaggc gacggcagga ccttccccaa gaggggccag 60

acatgcgtgg tgcactacac cggcatgctt ggcgacggca aaaaggtgga ctcaagcagg 120

gacaggaaca agcccttcaa gttcatgttg ggcaaacagg aggtgatcag aggctgggag 180

gagggtgttg cccagatgag cgtggggcag ggcgccaagc tcacgataag tcccgattac 240

gcctacggcg ccaccggtca ccccggcatc atccccccac acgccaccct ggtgttcgac 300

gtggaattgc tggagctgga g 321

<210> 89
<211> 477
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 89
atgatctctc tgattgcggc gctggcagtt gactacgtta ttggcatgga aaacgcgatg 60

ccatggaacc tcccggctga cctggcgtgg ttcaaacgta acaccctgaa caaacctgtg 120

atcatgggtc gtcacacctg ggaatctatt ggccgtcctc tcccgggtcg taaaaacatc 180

attctgtctt ctcagccagg caccgacgac cgtgttacct gggttaaaag cgttgacgaa 240

gcgattgctg cgtgcggtga tgttcctgaa attatggtga tcggcggtgg ccgtgttatc 300

gaacagttcc tgccgaaagc gcagaaactg tacctgaccc acatcgacgc ggaagttgaa 360

ggtgacaccc acttcccgga ctacgaaccg gatgattggg agagcgtatt ctccgaattc 420

catgatgcgg atgcgcaaaa ctctcattct tactgttttg aaatcctgga acgtcgt 477

<210> 90
<211> 236
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 90
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 tgacga 236

<210> 91
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 91
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> 92
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 92
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> 93
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 93
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> 94
<211> 1587
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 94
atgggcgtgc aggttgagac tataagccca ggcgacggca ggaccttccc caagaggggc 60

cagacatgcg tggtgcacta caccggcatg cttgaagacg gcaaaaaggt ggactcaagc 120

agggacagga acaagccctt caagttcatg ttgggcaaac aggaggtgat cagaggctgg 180

gaggagggtg ttgcccagat gagcgtgggg cagagggcca agctcacgat aagtcccgat 240

tacgcctacg gcgccaccgg tcaccccggc atcatccccc cacacgccac cctggtgttc 300

gacgtggaat tgctgaagcc cgagagcggc ggtggcagcg acgaggccga cagaaggctt 360

ttgagaaggt gcaggctccg gctggttgag gagctgcaag tcgaccaact gtgggacgcc 420

ctgctgtcca gggaactgtt taggccccac atgatcgagg acatccaaag agccgggtca 480

ggatctagga gggatcaggc taggcaactt attatcgatc tggaaaccag ggggagccaa 540

gcccttcccc tcttcatcag ctgtctcgag gatacgggcc aagacatgct cgccagtttt 600

ctgagaacga accgacaggc cgcaaagctg agtaaaccca ccctggagaa ccttacccct 660

gtggtactca ggcccgaaat ccggaagccc gaggtgctga ggccggagac tccgaggccc 720

gtggacatcg gcagtggggg gttcggtgac gtgggagcgc tggaaagcct gcgcggcaac 780

gctgacctcg cctacatcct tagcatggag ccgtgcggac actgtctgat catcaacaac 840

gtgaacttct gcagggagag cgggctgcgg accaggaccg ggagcaatat cgattgcgaa 900

aaactgagga ggaggttcag ctcactgcac ttcatggtgg aggtgaaggg cgacctgacc 960

gccaagaaga tggttctggc cttgcttgag cttgcgcagc aagatcacgg tgcccttgac 1020

tgttgtgtgg tggtgatact gagccacggc tgtcaggcca gccacctgca gtttccgggt 1080

gctgtctacg ggaccgacgg gtgccccgtg tctgtcgaaa agatagtgaa catcttcaac 1140

ggcacgtcct gcccctcact gggcggcaag cccaagctct tctttataca ggcttgcggt 1200

ggagagcaga aggaccatgg cttcgaggtg gccagcacca gccccgagga cgagagccct 1260

ggtagcaatc ccgagcccga tgccacccca tttcaagaag gattgaggac cttcgatcag 1320

ctcgacgcga ttagctctct gcccaccccc agcgacattt ttgtgagcta cagcacgttc 1380

ccgggtttcg tcagttggag ggaccctaag agcggaagct ggtatgtgga gacgctggac 1440

gacatattcg agcaatgggc acacagcgag gatctgcagt cactcctgtt gcgcgtggcc 1500

aacgccgttt ccgttaaggg catctataag cagatgccag gttgtttcaa tttcctccga 1560

aaaaagttgt tctttaagac cagctga 1587

<210> 95
<211> 1740
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 95
atgatctctc tgattgcggc gctggcagtt gactacgtta ttggcatgga aaacgcgatg 60

ccatggaacc tcccggctga cctggcgtgg ttcaaacgta acaccctgaa caaacctgtg 120

atcatgggtc gtcacacctg ggaatctatt ggccgtcctc tcccgggtcg taaaaacatc 180

attctgtctt ctcagccagg caccgacgac cgtgttacct gggttaaaag cgttgacgaa 240

gcgattgctg cgtgcggtga tgttcctgaa attatggtga tcggcggtgg ccgtgttatc 300

gaacagttcc tgccgaaagc gcagaaactg tacctgaccc acatcgacgc ggaagttgaa 360

ggtgacaccc acttcccgga ctacgaaccg gatgattggg agagcgtatt ctccgaattc 420

catgatgcgg atgcgcaaaa ctctcattct tactgttttg aaatcctgga acgtcgtagc 480

ggcggtggca gcgacgaggc cgacagaagg cttttgagaa ggtgcaggct ccggctggtt 540

gaggagctgc aagtcgacca actgtgggac gccctgctgt ccagggaact gtttaggccc 600

cacatgatcg aggacatcca aagagccggg tcaggatcta ggagggatca ggctaggcaa 660

cttattatcg atctggaaac caggggggagc caagcccttc ccctcttcat cagctgtctc 720

gaggatacgg gccaagacat gctcgccagt tttctgagaa cgaaccgaca ggccgcaaag 780

ctgagtaaac ccaccctgga gaaccttacc cctgtggtac tcaggcccga aatccggaag 840

cccgaggtgc tgaggccgga gactccgagg cccgtggaca tcggcagtgg ggggttcggt 900

gacgtgggag cgctggaaag cctgcgcggc aacgctgacc tcgcctacat ccttagcatg 960

gagccgtgcg gacactgtct gatcatcaac aacgtgaact tctgcaggga gagcgggctg 1020

cggaccagga ccgggagcaa tatcgattgc gaaaaactga ggaggaggtt cagctcactg 1080

cacttcatgg tggaggtgaa gggcgacctg accgccaaga agatggttct ggccttgctt 1140

gagcttgcgc agcaagatca cggtgccctt gactgttgtg tggtggtgat actgagccac 1200

ggctgtcagg ccagccacct gcagtttccg ggtgctgtct acgggaccga cgggtgcccc 1260

gtgtctgtcg aaaagatagt gaacatcttc aacggcacgt cctgcccctc actgggcggc 1320

aagcccaagc tcttctttat acaggcttgc ggtggagagc agaaggacca tggcttcgag 1380

gtggccagca ccagccccga ggacgagagc cctggtagca atcccgagcc cgatgccacc 1440

ccatttcaag aaggattgag gaccttcgat cagctcgacg cgattagctc tctgcccacc 1500

cccagcgaca tttttgtgag ctacagcacg ttcccgggtt tcgtcagttg gagggaccct 1560

aagagcggaa gctggtatgt ggagacgctg gacgacatat tcgagcaatg ggcacacagc 1620

gaggatctgc agtcactcct gttgcgcgtg gccaacgccg tttccgttaa gggcatctat 1680

aagcagatgc caggttgttt caatttcctc cgaaaaaagt tgttctttaa gaccagctga 1740

<210> 96
<211> 1824
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 96
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 tagcggcggt ggcagcgacg aggccgacag aaggcttttg 600

agaaggtgca ggctccggct ggttgaggag ctgcaagtcg accaactgtg ggacgccctg 660

ctgtccaggg aactgtttag gccccacatg atcgaggaca tccaaagagc cgggtcagga 720

tctaggaggg atcaggctag gcaacttatt atcgatctgg aaaccagggg gagccaagcc 780

cttcccctct tcatcagctg tctcgaggat acgggccaag acatgctcgc cagttttctg 840

agaacgaacc gacaggccgc aaagctgagt aaacccaccc tggagaacct tacccctgtg 900

gtactcaggc ccgaaatccg gaagcccgag gtgctgaggc cggagactcc gaggcccgtg 960

gacatcggca gtgggggttt cggtgacgtg ggagcgctgg aaagcctgcg cggcaacgct 1020

gacctcgcct acatccttag catggagccg tgcggacact gtctgatcat caacaacgtg 1080

aacttctgca gggagagcgg gctgcggacc aggaccggga gcaatatcga ttgcgaaaaa 1140

ctgaggagga ggttcagctc actgcacttc atggtggagg tgaagggcga cctgaccgcc 1200

aagaagatgg ttctggcctt gcttgagctt gcgcagcaag atcacggtgc ccttgactgt 1260

tgtgtggtgg tgatactgag ccacggctgt caggccagcc acctgcagtt tccgggtgct 1320

gtctacggga ccgacgggtg ccccgtgtct gtcgaaaaga tagtgaacat cttcaacggc 1380

acgtcctgcc cctcactggg cggcaagccc aagctcttct ttatacaggc ttgcggtgga 1440

gagcagaagg accatggctt cgaggtggcc agcaccagcc ccgaggacga gagccctggt 1500

agcaatcccg agcccgatgc caccccattt caagaaggat tgaggacctt cgatcagctc 1560

gacgcgatta gctctctgcc caccccagc gacatttttg tgagctacag cacgttcccg 1620

ggtttcgtca gttggaggga ccctaagagc ggaagctggt atgtggagac gctggacgac 1680

atattcgagc aatgggcaca cagcgaggat ctgcagtcac tcctgttgcg cgtggccaac 1740

gccgtttccg ttaagggcat ctataagcag atgccaggtt gtttcaattt cctccgaaaa 1800

aagttgttct ttaagaccag ctga 1824

<210> 97
<211> 1824
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 97
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 tagcggcggt ggcagcgacg aggccgacag aaggcttttg 600

agaaggtgca ggctccggct ggttgaggag ctgcaagtcg accaactgtg ggacgccctg 660

ctgtccaggg aactgtttag gccccacatg atcgaggaca tccaaagagc cgggtcagga 720

tctaggaggg atcaggctag gcaacttatt atcgatctgg aaaccagggg gagccaagcc 780

cttcccctct tcatcagctg tctcgaggat acgggccaag acatgctcgc cagttttctg 840

agaacgaacc gacaggccgc aaagctgagt aaacccaccc tggagaacct tacccctgtg 900

gtactcaggc ccgaaatccg gaagcccgag gtgctgaggc cggagactcc gaggcccgtg 960

gacatcggca gtgggggttt cggtgacgtg ggagcgctgg aaagcctgcg cggcaacgct 1020

gacctcgcct acatccttag catggagccg tgcggacact gtctgatcat caacaacgtg 1080

aacttctgca gggagagcgg gctgcggacc aggaccggga gcaatatcga ttgcgaaaaa 1140

ctgaggagga ggttcagctc actgcacttc atggtggagg tgaagggcga cctgaccgcc 1200

aagaagatgg ttctggcctt gcttgagctt gcgcagcaag atcacggtgc ccttgactgt 1260

tgtgtggtgg tgatactgag ccacggctgt caggccagcc acctgcagtt tccgggtgct 1320

gtctacggga ccgacgggtg ccccgtgtct gtcgaaaaga tagtgaacat cttcaacggc 1380

acgtcctgcc cctcactggg cggcaagccc aagctcttct ttatacaggc ttgcggtgga 1440

gagcagaagg accatggctt cgaggtggcc agcaccagcc ccgaggacga gagccctggt 1500

agcaatcccg agcccgatgc caccccattt caagaaggat tgaggacctt cgatcagctc 1560

gacgcgatta gctctctgcc caccccagc gacatttttg tgagctacag cacgttcccg 1620

ggtttcgtca gttggaggga ccctaagagc ggaagctggt atgtggagac gctggacgac 1680

atattcgagc aatgggcaca cagcgaggat ctgcagtcac tcctgttgcg cgtggccaac 1740

gccgtttccg ttaagggcat ctataagcag atgccaggtt gtttcaattt cctccgaaaa 1800

aagttgttct ttaagaccag ctga 1824

<210> 98
<211> 1824
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 98
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 tagcggcggt ggcagcgacg aggccgacag aaggcttttg 600

agaaggtgca ggctccggct ggttgaggag ctgcaagtcg accaactgtg ggacgccctg 660

ctgtccaggg aactgtttag gccccacatg atcgaggaca tccaaagagc cgggtcagga 720

tctaggaggg atcaggctag gcaacttatt atcgatctgg aaaccagggg gagccaagcc 780

cttcccctct tcatcagctg tctcgaggat acgggccaag acatgctcgc cagttttctg 840

agaacgaacc gacaggccgc aaagctgagt aaacccaccc tggagaacct tacccctgtg 900

gtactcaggc ccgaaatccg gaagcccgag gtgctgaggc cggagactcc gaggcccgtg 960

gacatcggca gtgggggttt cggtgacgtg ggagcgctgg aaagcctgcg cggcaacgct 1020

gacctcgcct acatccttag catggagccg tgcggacact gtctgatcat caacaacgtg 1080

aacttctgca gggagagcgg gctgcggacc aggaccggga gcaatatcga ttgcgaaaaa 1140

ctgaggagga ggttcagctc actgcacttc atggtggagg tgaagggcga cctgaccgcc 1200

aagaagatgg ttctggcctt gcttgagctt gcgcagcaag atcacggtgc ccttgactgt 1260

tgtgtggtgg tgatactgag ccacggctgt caggccagcc acctgcagtt tccgggtgct 1320

gtctacggga ccgacgggtg ccccgtgtct gtcgaaaaga tagtgaacat cttcaacggc 1380

acgtcctgcc cctcactggg cggcaagccc aagctcttct ttatacaggc ttgcggtgga 1440

gagcagaagg accatggctt cgaggtggcc agcaccagcc ccgaggacga gagccctggt 1500

agcaatcccg agcccgatgc caccccattt caagaaggat tgaggacctt cgatcagctc 1560

gacgcgatta gctctctgcc caccccagc gacatttttg tgagctacag cacgttcccg 1620

ggtttcgtca gttggaggga ccctaagagc ggaagctggt atgtggagac gctggacgac 1680

atattcgagc aatgggcaca cagcgaggat ctgcagtcac tcctgttgcg cgtggccaac 1740

gccgtttccg ttaagggcat ctataagcag atgccaggtt gtttcaattt cctccgaaaa 1800

aagttgttct ttaagaccag ctga 1824

<210> 99

<211> 1242
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 99
atgctggagg gcgtgcaggt tgagactata agcccaggcg acggcaggac cttccccaag 60

aggggccaga catgcgtggt gcactacacc ggcatgcttg aagacggcaa aaaggtggac 120

tcaagcaggg acaggaacaa gcccttcaag ttcatgttgg gcaaacagga ggtgatcaga 180

ggctgggagg agggtgttgc ccagatgagc gtggggcaga gggccaagct cacgataagt 240

cccgattacg cctacggcgc caccggtcac cccggcatca tccccccaca cgccaccctg 300

gtgttcgacg tggaattgct gaagctggag agcggcggtg gcagcggcgt ggacgggttc 360

ggtgacgtgg gagcgctgga aagcctgcgc ggcaacgctg acctcgccta catccttagc 420

atggagccgt gcggacactg tctgatcatc aacaacgtga acttctgcag ggagagcggg 480

ctgcggacca ggaccgggag caatatcgat tgcgaaaaac tgaggaggag gttcagctca 540

ctgcacttca tggtggaggt gaagggcgac ctgaccgcca agaagatggt tctggccttg 600

cttgagcttg cgcggcaaga tcacggtgcc cttgactgtt gtgtggtggt gatactgagc 660

cacggctgtc aggccagcca cctgcagttt ccgggtgctg tctacgggac cgacgggtgc 720

cccgtgtctg tcgaaaagat agtgaacatc ttcaacggca cgtcctgccc ctcactgggc 780

ggcaagccca agctcttctt tatacaggct tgcggtggag agcagaagga ccatggcttc 840

gaggtggcca gcaccagccc cgaggacgag agccctggta gcaatcccga gcccgatgcc 900

accccatttc aagaaggatt gaggaccttc gatcagctcg acgcgattag ctctctgccc 960

acccccagcg acatttttgt gagctacagc acgttcccgg gtttcgtcag ttggagggac 1020

cctaagagcg gaagctggta tgtggagacg ctggacgaca tattcgagca atgggcacac 1080

agcgaggatc tgcagtcact cctgttgcgc gtggccaacg ccgtttccgt taagggcatc 1140

tataagcaga tgccaggttg tttcaatttc ctccgaaaaa agttgttctt taagaccagc 1200

cagctgatag ggatgctaca aggcctgatg cgtgacctgt ga 1242

<210> 100
<211> 1578
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 100
atggacgagg ccgacagaag gcttttgaga aggtgcaggc tccggctggt tgaggagctg 60

caagtcgacc aactgtggga cgccctgctg tccagggaac tgtttaggcc ccacatgatc 120

gaggacatcc aaagagccgg gtcaggatct aggagggatc aggctaggca acttattatc 180

gatctggaaa ccaggggggag ccaagccctt cccctcttca tcagctgtct cgaggatacg 240

ggccaagaca tgctcgccag ttttctgaga acgaaccgac aggccgcaaa gctgagtaaa 300

cccaccctgg agaaccttac ccctgtggta ctcaggcccg aaatccggaa gcccgaggtg 360

ctgaggccgg agactccgag gcccgtggac atcggcagtg gggggttcgg tgacgtggga 420

gcgctggaaa gcctgcgcgg caacgctgac ctcgcctaca tccttagcat ggagccgtgc 480

ggacactgtc tgatcatcaa caacgtgaac ttctgcaggg agagcgggct gcggaccagg 540

accgggagca atatcgattg cgaaaaactg aggaggaggt tcagctcact gcacttcatg 600

gtggaggtga agggcgacct gaccgccaag aagatggttc tggccttgct tgagcttgcg 660

cagcaagatc acggtgccct tgactgttgt gtggtggtga tactgagcca cggctgtcag 720

gccagccacc tgcagtttcc gggtgctgtc tacgggaccg acgggtgccc cgtgtctgtc 780

gaaaagatag tgaacatctt caacggcacg tcctgcccct cactgggcgg caagcccaag 840

ctcttcttta tacaggcttg cggtggagag cagaaggacc atggcttcga ggtggccagc 900

accagccccg aggacgagag ccctggtagc aatcccgagc ccgatgccac cccatttcaa 960

gaaggattga ggaccttcga tcagctcgac gcgattagct ctctgcccac ccccagcgac 1020

atttttgtga gctacagcac gttcccgggt ttcgtcagtt ggagggaccc taagagcgga 1080

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cagtcactcc tgttgcgcgt ggccaacgcc gtttccgtta agggcatcta taagcagatg 1200

ccaggttgtt tcaatttcct ccgaaaaaag ttgttcttta agaccagcag cggcggcgtg 1260

caggttgaga ctataagccc aggcgacggc aggaccttcc ccaagagggg ccagacatgc 1320

gtggtgcact acaccggcat gcttggcgac ggcaaaaagg tggactcaag cagggacagg 1380

aacaagccct tcaagttcat gttgggcaaa caggaggtga tcagaggctg ggaggagggt 1440

gttgcccaga tgagcgtggg gcagggcgcc aagctcacga taagtcccga ttacgcctac 1500

ggcgccaccg gtcaccccgg catcatcccc ccacacgcca ccctggtgtt cgacgtggaa 1560

ttgctggagc tggagtga 1578

<210> 101
<211> 1731
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 101
atggacgagg ccgacagaag gcttttgaga aggtgcaggc tccggctggt tgaggagctg 60

caagtcgacc aactgtggga cgccctgctg tccagggaac tgtttaggcc ccacatgatc 120

gaggacatcc aaagagccgg gtcaggatct aggagggatc aggctaggca acttattatc 180

gatctggaaa ccaggggggag ccaagccctt cccctcttca tcagctgtct cgaggatacg 240

ggccaagaca tgctcgccag ttttctgaga acgaaccgac aggccgcaaa gctgagtaaa 300

cccaccctgg agaaccttac ccctgtggta ctcaggcccg aaatccggaa gcccgaggtg 360

ctgaggccgg agactccgag gcccgtggac atcggcagtg gggggttcgg tgacgtggga 420

gcgctggaaa gcctgcgcgg caacgctgac ctcgcctaca tccttagcat ggagccgtgc 480

ggacactgtc tgatcatcaa caacgtgaac ttctgcaggg agagcgggct gcggaccagg 540

accgggagca atatcgattg cgaaaaactg aggaggaggt tcagctcact gcacttcatg 600

gtggaggtga agggcgacct gaccgccaag aagatggttc tggccttgct tgagcttgcg 660

cagcaagatc acggtgccct tgactgttgt gtggtggtga tactgagcca cggctgtcag 720

gccagccacc tgcagtttcc gggtgctgtc tacgggaccg acgggtgccc cgtgtctgtc 780

gaaaagatag tgaacatctt caacggcacg tcctgcccct cactgggcgg caagcccaag 840

ctcttcttta tacaggcttg cggtggagag cagaaggacc atggcttcga ggtggccagc 900

accagccccg aggacgagag ccctggtagc aatcccgagc ccgatgccac cccatttcaa 960

gaaggattga ggaccttcga tcagctcgac gcgattagct ctctgcccac ccccagcgac 1020

atttttgtga gctacagcac gttcccgggt ttcgtcagtt ggagggaccc taagagcgga 1080

agctggtatg tggagacgct ggacgacata ttcgagcaat gggcacacag cgaggatctg 1140

cagtcactcc tgttgcgcgt ggccaacgcc gtttccgtta agggcatcta taagcagatg 1200

ccaggttgtt tcaatttcct ccgaaaaaag ttgttcttta agaccagcag cggcatctct 1260

ctgattgcgg cgctggcagt tgactacgtt attggcatgg aaaacgcgat gccatggaac 1320

ctcccggctg acctggcgtg gttcaaacgt aacaccctga acaaacctgt gatcatgggt 1380

cgtcacacct gggaatctat tggccgtcct ctcccgggtc gtaaaaacat cattctgtct 1440

tctcagccag gcaccgacga ccgtgttacc tgggttaaaa gcgttgacga agcgattgct 1500

gcgtgcggtg atgttcctga aattatggtg atcggcggtg gccgtgttat cgaacagttc 1560

ctgccgaaag cgcagaaact gtacctgacc cacatcgacg cggaagttga aggtgacacc 1620

cacttcccgg actacgaacc ggatgattgg gagagcgtat tctccgaatt ccatgatgcg 1680

gatgcgcaaa actctcattc ttactgtttt gaaatcctgg aacgtcgttg a 1731

<210> 102
<211> 1731
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 102
atggacgagg ccgacagaag gcttttgaga aggtgcaggc tccggctggt tgaggagctg 60

caagtcgacc aactgtggga cgccctgctg tccagggaac tgtttaggcc ccacatgatc 120

gaggacatcc aaagagccgg gtcaggatct aggagggatc aggctaggca acttattatc 180

gatctggaaa ccagggggag ccaagccctt cccctcttca tcagctgtct cgaggatacg 240

ggccaagaca tgctcgccag ttttctgaga acgaaccgac aggccgcaaa gctgagtaaa 300

cccaccctgg agaaccttac ccctgtggta ctcaggcccg aaatccggaa gcccgaggtg 360

ctgaggccgg agactccgag gcccgtggac atcggcagtg gggggttcgg tgacgtggga 420

gcgctggaaa gcctgcgcgg caacgctgac ctcgcctaca tccttagcat ggagccgtgc 480

ggacactgtc tgatcatcaa caacgtgaac ttctgcaggg agagcgggct gcggaccagg 540

accgggagca atatcgattg cgaaaaactg aggaggaggt tcagctcact gcacttcatg 600

gtggaggtga agggcgacct gaccgccaag aagatggttc tggccttgct tgagcttgcg 660

cagcaagatc acggtgccct tgactgttgt gtggtggtga tactgagcca cggctgtcag 720

gccagccacc tgcagtttcc gggtgctgtc tacgggaccg acgggtgccc cgtgtctgtc 780

gaaaagatag tgaacatctt caacggcacg tcctgcccct cactgggcgg caagcccaag 840

ctcttcttta tacaggcttg cggtggagag cagaaggacc atggcttcga ggtggccagc 900

accagccccg aggacgagag ccctggtagc aatcccgagc ccgatgccac cccatttcaa 960

gaaggattga ggaccttcga tcagctcgac gcgattagct ctctgcccac ccccagcgac 1020

atttttgtga gctacagcac gttcccgggt ttcgtcagtt ggagggaccc taagagcgga 1080

agctggtatg tggagacgct ggacgacata ttcgagcaat gggcacacag cgaggatctg 1140

cagtcactcc tgttgcgcgt ggccaacgcc gtttccgtta agggcatcta taagcagatg 1200

ccaggttgtt tcaatttcct ccgaaaaaag ttgttcttta agaccagcag cggcatctct 1260

ctgattgcgg cgctggcagt tgactacgtt attggcatgg aaaacgcgat gccatggaac 1320

ctcccggctg acctggcgtg gttcaaacgt aacaccctga acaaacctgt gatcatgggt 1380

cgtcacacct gggaatctat tggccgtcct ctcccgggtc gtaaaaacat cattctgtct 1440

tctcagccag gcaccgacga ccgtgttacc tgggttaaaa gcgttgacga agcgattgct 1500

gcgtgcggtg atgttcctga aattatggtg atcggcggtg gccgtgttta cgaacagttc 1560

ctgccgaaag cgcagaaact gtacctgacc cacatcgacg cggaagttga aggtgacacc 1620

cacttcccgg actacaaacc ggatgattgg gagagcgtat tctccgaatt ccatgatgcg 1680

gatgcgcaaa actctcattc ttactgtttt gaaatcctgg aacgtcgttg a 1731

<210> 103
<211> 431
<212> PRT
<213> Homo sapiens

<400> 103

```
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1               5                  10                  15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
            20                  25                  30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
        35                  40                  45

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

Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala
65                  70                  75                  80

Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu
                85                  90                  95

Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His
            100                 105                 110

Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met
        115                 120                 125

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

Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp
145                 150                 155                 160

Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala
                165                 170                 175

Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro
            180                 185                 190

Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe
        195                 200                 205
```

```
Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu
    210                 215                 220

Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln
225                 230                 235                 240

Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met
                245                 250                 255

Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val
            260                 265                 270

Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln
        275                 280                 285

Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser
    290                 295                 300

Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr
305                 310                 315                 320

Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met
                325                 330                 335

Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu
            340                 345                 350

Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr
        355                 360                 365

Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala
    370                 375                 380

Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser
385                 390                 395                 400

Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys
                405                 410                 415
```

Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
420 425 430

<210> 104
<211> 430
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Payload sequence

<400> 104
Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu Gly
1 5 10 15

Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala Ser
20 25 30

Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg Asp
35 40 45

Leu Arg Gly Gly Ala His Ala Ser Ser Ser Ser Leu Asn Pro Met Pro
50 55 60

Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala Pro
65 70 75 80

Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu Gln
85 90 95

Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His Ala
100 105 110

Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile
115 120 125

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

Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val

```
145                 150                 155                 160

Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro
                165                 170                 175

Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu
            180                 185                 190

Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu
        195                 200                 205

Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp
    210                 215                 220

Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser
225                 230                 235                 240

Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln
                245                 250                 255

Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala
            260                 265                 270

Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly
        275                 280                 285

Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu
    290                 295                 300

Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe
305                 310                 315                 320

Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg
                325                 330                 335

Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala
            340                 345                 350

Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg
```

355 360 365

Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile
370 375 380

Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu
385 390 395 400

Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg
405 410 415

Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
420 425 430

<210> 105
<211> 396
<212> PRT
<213> Homo sapiens

<400> 105
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1 5 10 15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
20 25 30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
35 40 45

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

Pro Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr
65 70 75 80

Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu
85 90 95

Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro
100 105 110

```
Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg
        115                 120                 125

Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys
    130                 135                 140

Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala
145                 150                 155                 160

Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro
                165                 170                 175

Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys
            180                 185                 190

Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu
        195                 200                 205

Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His
    210                 215                 220

Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser
225                 230                 235                 240

Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val
                245                 250                 255

Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala
            260                 265                 270

Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu
        275                 280                 285

Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro
    290                 295                 300

Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu
305                 310                 315                 320
```

Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe
325 330 335

Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His
340 345 350

Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly
355 360 365

Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln
370 375 380

Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
385 390 395

<210> 106
<211> 395
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 106
Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu Gly
1 5 10 15

Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala Ser
20 25 30

Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg Asp
35 40 45

Leu Arg Gly Gly Ala His Ala Ser Ser Ser Ser Leu Asn Pro Met Pro
50 55 60

Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr Pro
65 70 75 80

Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu Thr

85 90 95

Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro Gly
100 105 110

Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg Glu
115 120 125

Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys Asp
130 135 140

Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala Asn
145 150 155 160

Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro Glu
165 170 175

Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys Gly
180 185 190

Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu Gln
195 200 205

Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His Leu
210 215 220

Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser Asp
225 230 235 240

Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val Val
245 250 255

Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala Val
260 265 270

Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu Phe
275 280 285

Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro Phe

290 295 300

Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu Lys
305 310 315 320

Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe Ala
325 330 335

Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His Asn
340 345 350

Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly Ala
355 360 365

Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln Arg
370 375 380

Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
385 390 395

<210> 107
<211> 431
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 107
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1 5 10 15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
20 25 30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
35 40 45

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

```
Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala
65                  70                  75                  80

Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu
                85                  90                  95

Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His
            100                 105                 110

Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met
        115                 120                 125

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

Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp
145                 150                 155                 160

Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala
                165                 170                 175

Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro
            180                 185                 190

Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe
        195                 200                 205

Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu
    210                 215                 220

Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln
225                 230                 235                 240

Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met
                245                 250                 255

Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val
            260                 265                 270
```

```
Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln
        275                 280                 285


Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser
    290                 295                 300


Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr
305                 310                 315                 320


Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met
                325                 330                 335


Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu
            340                 345                 350


Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr
        355                 360                 365


Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala
    370                 375                 380


Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser
385                 390                 395                 400


Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys
                405                 410                 415


Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
            420                 425                 430


<210> 108
<211> 396
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Construct

<400> 108
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
```

```
1               5                   10                  15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
            20                  25                  30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
        35                  40                  45

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

Pro Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr
65                  70                  75                  80

Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu
                85                  90                  95

Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro
            100                 105                 110

Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg
        115                 120                 125

Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys
    130                 135                 140

Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala
145                 150                 155                 160

Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro
                165                 170                 175

Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys
            180                 185                 190

Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu
        195                 200                 205

Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His
```

210 215 220

Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser
225 230 235 240

Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val
245 250 255

Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala
260 265 270

Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu
275 280 285

Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro
290 295 300

Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu
305 310 315 320

Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe
325 330 335

Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His
340 345 350

Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly
355 360 365

Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln
370 375 380

Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
385 390 395

<210> 109
<211> 543
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 109

```
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 Ser Gly Gly Gly
            100                 105                 110

Ser Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
        115                 120                 125

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
    130                 135                 140

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

Asp Leu Arg Gly Gly Ala His Ala Ser Ser Ser Ser Leu Asn Pro Met
                165                 170                 175

Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala
            180                 185                 190
```

```
Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu
        195                 200                 205

Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His
    210                 215                 220

Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met
225                 230                 235                 240

Ile Ser Leu Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys
                245                 250                 255

Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp
            260                 265                 270

Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala
        275                 280                 285

Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro
    290                 295                 300

Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe
305                 310                 315                 320

Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu
                325                 330                 335

Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln
            340                 345                 350

Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met
        355                 360                 365

Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val
    370                 375                 380

Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln
385                 390                 395                 400
```

```
Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser
                405                 410                 415


Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr
            420                 425                 430


Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met
        435                 440                 445


Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu
    450                 455                 460


Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr
465                 470                 475                 480


Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala
                485                 490                 495


Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser
            500                 505                 510


Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys
        515                 520                 525


Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
    530                 535                 540


<210> 110
<211> 594
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Construct

<400> 110
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 Ser
145                 150                 155                 160

Gly Gly Gly Ser Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser
                165                 170                 175

Leu Ala Leu Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala
            180                 185                 190

Pro Lys Ala Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe
        195                 200                 205

Gln Gly Arg Asp Leu Arg Gly Gly Ala His Ala Ser Ser Ser Ser Leu
    210                 215                 220

Asn Pro Met Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val
```

225 230 235 240

Met Val Ala Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln
245 250 255

Ala Leu Leu Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val
260 265 270

Asp Ala His Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser
275 280 285

Pro Ala Met Ile Ser Leu Thr Pro Pro Thr Thr Ala Thr Gly Val Phe
290 295 300

Ser Leu Lys Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser
305 310 315 320

Leu Glu Trp Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn
325 330 335

Pro Ser Ala Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser
340 345 350

Ser Tyr Pro Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu
355 360 365

Lys Val Phe Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp
370 375 380

His Leu Leu Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu
385 390 395 400

Met Val Gln Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu
405 410 415

Ser Ala Met Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala
420 425 430

Ser Ser Val Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala

435 440 445

Gly Ser Gln Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala
450 455 460

Pro Asp Ser Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly
465 470 475 480

Asn Ser Thr Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe
485 490 495

His Asn Met Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala
500 505 510

Ile Leu Glu Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His
515 520 525

Trp Phe Thr Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp
530 535 540

Lys Asn Ala Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg
545 550 555 560

Val Glu Ser Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe
565 570 575

Arg Lys Lys Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro
580 585 590

Gly Pro

<210> 111
<211> 540
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 111

```
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1               5                  10                  15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
            20                  25                  30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
        35                  40                  45

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

Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala
65                  70                  75                  80

Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu
                85                  90                  95

Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His
            100                 105                 110

Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met
        115                 120                 125

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

Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp
145                 150                 155                 160

Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala
                165                 170                 175

Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro
            180                 185                 190

Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe
        195                 200                 205
```

```
Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu
    210                 215                 220

Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln
225                 230                 235                 240

Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met
                245                 250                 255

Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val
            260                 265                 270

Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln
        275                 280                 285

Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser
    290                 295                 300

Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr
305                 310                 315                 320

Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met
                325                 330                 335

Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu
            340                 345                 350

Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr
        355                 360                 365

Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala
    370                 375                 380

Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser
385                 390                 395                 400

Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys
                405                 410                 415
```

```
Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro Ser
            420                 425                 430

Gly Gly Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe
        435                 440                 445

Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly
    450                 455                 460

Asp Gly Lys Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys
465                 470                 475                 480

Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val
                485                 490                 495

Ala Gln Met Ser Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp
            500                 505                 510

Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala
        515                 520                 525

Thr Leu Val Phe Asp Val Glu Leu Leu Glu Leu Glu
    530                 535                 540


<210> 112
<211> 591
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Construct

<400> 112
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1               5                   10                  15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
            20                  25                  30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
```

```
        35                  40                  45

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

Pro Pro Ser Gln Leu Gln Leu Pro Thr Leu Pro Leu Val Met Val Ala
65                  70                  75                  80

Pro Ser Gly Ala Arg Leu Gly Pro Leu Pro His Leu Gln Ala Leu Leu
                85                  90                  95

Gln Asp Arg Pro His Phe Met His Gln Leu Ser Thr Val Asp Ala His
            100                 105                 110

Ala Arg Thr Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met
        115                 120                 125

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

Ala Arg Pro Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp
145                 150                 155                 160

Val Ser Arg Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala
                165                 170                 175

Pro Arg Lys Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro
            180                 185                 190

Leu Leu Ala Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe
        195                 200                 205

Glu Glu Pro Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu
    210                 215                 220

Asp Glu Lys Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln
225                 230                 235                 240

Ser Leu Glu Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met
```

245 250 255

Gln Ala His Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val
260 265 270

Ala Ser Ser Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln
275 280 285

Gly Pro Val Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser
290 295 300

Leu Phe Ala Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr
305 310 315 320

Phe Pro Glu Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met
325 330 335

Arg Pro Pro Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu
340 345 350

Ala Pro Glu Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr
355 360 365

Arg Met Phe Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala
370 375 380

Ile Arg His Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser
385 390 395 400

Glu Lys Gly Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys
405 410 415

Arg Ser Gln Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro Ser
420 425 430

Gly Ile Ser Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met
435 440 445

Glu Asn Ala Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys

450 455 460

Arg Asn Thr Leu Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu
465 470 475 480

Ser Ile Gly Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser
485 490 495

Gln Pro Gly Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu
500 505 510

Ala Ile Ala Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly
515 520 525

Gly Arg Val Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu
530 535 540

Thr His Ile Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr
545 550 555 560

Glu Pro Asp Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp
565 570 575

Ala Gln Asn Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
580 585 590

<210> 113
<211> 505
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 113
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 Ser Gly Pro Asn
            100                 105                 110

Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu Gly Pro Ser
        115                 120                 125

Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala Ser Asp Leu
    130                 135                 140

Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg Asp Leu Arg
145                 150                 155                 160

Gly Gly Ala His Ala Ser Ser Ser Ser Leu Asn Pro Met Pro Pro Ser
                165                 170                 175

Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr Pro Val Leu
            180                 185                 190

Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu Thr Pro Pro
        195                 200                 205

Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro Gly Leu Pro
    210                 215                 220

Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg Glu Pro Ala
225                 230                 235                 240
```

```
Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys Asp Ser Thr
                245                 250                 255

Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala Asn Gly Val
            260                 265                 270

Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro Glu Asp Phe
        275                 280                 285

Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys Gly Arg Ala
    290                 295                 300

Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu Gln Gln Leu
305                 310                 315                 320

Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His Leu Ala Gly
                325                 330                 335

Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser Asp Lys Gly
            340                 345                 350

Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val Val Pro Ala
        355                 360                 365

Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala Val Arg Arg
    370                 375                 380

His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu Phe Leu His
385                 390                 395                 400

Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro Phe Thr Tyr
                405                 410                 415

Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu Lys Gln Arg
            420                 425                 430

Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe Ala Phe Phe
        435                 440                 445
```

```
Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His Asn Leu Ser
    450                 455                 460


Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly Ala Val Trp
465                 470                 475                 480


Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln Arg Pro Ser
                485                 490                 495


Arg Cys Ser Asn Pro Thr Pro Gly Pro
            500                 505


<210> 114
<211> 556
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Construct

<400> 114
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 Ser
145 150 155 160

Gly Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
165 170 175

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
180 185 190

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
195 200 205

Asp Leu Arg Gly Gly Ala His Ala Ser Ser Ser Ser Leu Asn Pro Met
210 215 220

Pro Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr
225 230 235 240

Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu
245 250 255

Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro
260 265 270

Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg
275 280 285

Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys
290 295 300

Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala

305 310 315 320

Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro
325 330 335

Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys
340 345 350

Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu
355 360 365

Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His
370 375 380

Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser
385 390 395 400

Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val
405 410 415

Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala
420 425 430

Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu
435 440 445

Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro
450 455 460

Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu
465 470 475 480

Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe
485 490 495

Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His
500 505 510

Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly

515 520 525

Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln
530 535 540

Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro
545 550 555

<210> 115
<211> 505
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 115
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1 5 10 15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
20 25 30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
35 40 45

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

Pro Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr
65 70 75 80

Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu
85 90 95

Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro
100 105 110

Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg
115 120 125

```
Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys
    130                 135                 140

Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala
145                 150                 155                 160

Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro
                165                 170                 175

Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys
            180                 185                 190

Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu
        195                 200                 205

Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His
    210                 215                 220

Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser
225                 230                 235                 240

Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val
                245                 250                 255

Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala
            260                 265                 270

Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu
        275                 280                 285

Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro
    290                 295                 300

Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu
305                 310                 315                 320

Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe
                325                 330                 335
```

```
Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His
            340                 345                 350

Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly
        355                 360                 365

Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln
    370                 375                 380

Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro Ser Gly Gly Val
385                 390                 395                 400

Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg
                405                 410                 415

Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Gly Asp Gly Lys
            420                 425                 430

Lys Val Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu
        435                 440                 445

Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met
    450                 455                 460

Ser Val Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr
465                 470                 475                 480

Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val
                485                 490                 495

Phe Asp Val Glu Leu Leu Glu Leu Glu
            500                 505


<210> 116
<211> 556
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
```

Construct

<400> 116

```
Met Pro Asn Pro Arg Pro Gly Lys Pro Ser Ala Pro Ser Leu Ala Leu
1               5                  10                  15

Gly Pro Ser Pro Gly Ala Ser Pro Ser Trp Arg Ala Ala Pro Lys Ala
            20                  25                  30

Ser Asp Leu Leu Gly Ala Arg Gly Pro Gly Gly Thr Phe Gln Gly Arg
        35                  40                  45

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

Pro Pro Ser Gln Leu Gln Leu Ser Thr Val Asp Ala His Ala Arg Thr
65                  70                  75                  80

Pro Val Leu Gln Val His Pro Leu Glu Ser Pro Ala Met Ile Ser Leu
                85                  90                  95

Thr Pro Pro Thr Thr Ala Thr Gly Val Phe Ser Leu Lys Ala Arg Pro
            100                 105                 110

Gly Leu Pro Pro Gly Ile Asn Val Ala Ser Leu Glu Trp Val Ser Arg
        115                 120                 125

Glu Pro Ala Leu Leu Cys Thr Phe Pro Asn Pro Ser Ala Pro Arg Lys
    130                 135                 140

Asp Ser Thr Leu Ser Ala Val Pro Gln Ser Ser Tyr Pro Leu Leu Ala
145                 150                 155                 160

Asn Gly Val Cys Lys Trp Pro Gly Cys Glu Lys Val Phe Glu Glu Pro
                165                 170                 175

Glu Asp Phe Leu Lys His Cys Gln Ala Asp His Leu Leu Asp Glu Lys
            180                 185                 190

Gly Arg Ala Gln Cys Leu Leu Gln Arg Glu Met Val Gln Ser Leu Glu
```

```
        195                 200                 205

Gln Gln Leu Val Leu Glu Lys Glu Lys Leu Ser Ala Met Gln Ala His
    210                 215                 220

Leu Ala Gly Lys Met Ala Leu Thr Lys Ala Ser Ser Val Ala Ser Ser
225                 230                 235                 240

Asp Lys Gly Ser Cys Cys Ile Val Ala Ala Gly Ser Gln Gly Pro Val
                245                 250                 255

Val Pro Ala Trp Ser Gly Pro Arg Glu Ala Pro Asp Ser Leu Phe Ala
            260                 265                 270

Val Arg Arg His Leu Trp Gly Ser His Gly Asn Ser Thr Phe Pro Glu
        275                 280                 285

Phe Leu His Asn Met Asp Tyr Phe Lys Phe His Asn Met Arg Pro Pro
    290                 295                 300

Phe Thr Tyr Ala Thr Leu Ile Arg Trp Ala Ile Leu Glu Ala Pro Glu
305                 310                 315                 320

Lys Gln Arg Thr Leu Asn Glu Ile Tyr His Trp Phe Thr Arg Met Phe
                325                 330                 335

Ala Phe Phe Arg Asn His Pro Ala Thr Trp Lys Asn Ala Ile Arg His
            340                 345                 350

Asn Leu Ser Leu His Lys Cys Phe Val Arg Val Glu Ser Glu Lys Gly
        355                 360                 365

Ala Val Trp Thr Val Asp Glu Leu Glu Phe Arg Lys Lys Arg Ser Gln
    370                 375                 380

Arg Pro Ser Arg Cys Ser Asn Pro Thr Pro Gly Pro Ser Gly Ile Ser
385                 390                 395                 400

Leu Ile Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala
```

405 410 415

Met Pro Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr
420 425 430

Leu Asn Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly
435 440 445

Arg Pro Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly
450 455 460

Thr Asp Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala
465 470 475 480

Ala Cys Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val
485 490 495

Ile Glu Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile
500 505 510

Asp Ala Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp
515 520 525

Asp Trp Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn
530 535 540

Ser His Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
545 550 555

<210> 117
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 117
atgtacagga tgcagctgct gagctgcatc gccctgagcc tggccctggt gaccaacagc 60

<210> 118
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 118
atgtacagaa tgcagctgct gagctgcatc gccctgtccc tcgccctggt gaccaactcc 60

<210> 119
<211> 22
<212> PRT
<213> Homo sapiens

<400> 119
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> 120
<211> 66
<212> DNA
<213> Homo sapiens

<400> 120
atgtgtcacc agcagttggt catctcttgg ttttccctgg tttttctggc atctcccctc 60

gtggcc 66

<210> 121
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 121
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atcccctctg 60

gtggca 66

<210> 122
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 122
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc cagccctctg 60

gtggcc 66

<210> 123
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 123
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc aagccctctg 60

gtggca 66

<210> 124
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 124
atgtgccacc agcagctggt catcagctgg ttctccctgg tgtttctggc atccccactg 60

gtggca 66

<210> 125
<211> 66
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 125
atgtgccacc aacagctcgt gatcagctgg ttctccctgg tgttcctggc tagccccctg 60

gtggcc 66

<210> 126
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 126
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc ctccccccctg 60

gtggcc 66

<210> 127
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 127
atgtgccacc agcagctggt catctcctgg ttctctctgg tgtttctggc atctcctctg 60

gtggca 66

<210> 128
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 128
atgtgccacc agcagctggt catctcttgg ttcagcctgg tgtttctggc atccccactg 60

gtggca 66

<210> 129
<211> 18
<212> PRT
<213> Homo sapiens

<400> 129
Met Asp Trp Thr Trp Ile Leu Phe Leu Val Ala Ala Ala Thr Arg Val
1   5   10   15

His Ser

<210> 130
<211> 54
<212> DNA
<213> Homo sapiens

<400> 130
atggactgga catggatact cttcctggta gcagccgcca cacgagtgca cagc 54

<210> 131
<211> 21
<212> PRT
<213> Homo sapiens

<400> 131
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> 132
<211> 63
<212> DNA
<213> Homo sapiens

<400> 132
atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg 60

ccg 63

<210> 133
<211> 63

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 133
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccagg 60

ccc 63

<210> 134
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 134
atggcactgc cagtgacagc cctgctgctg cctctggccc tgctgctgca cgcagccaga 60

cct 63

<210> 135
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 135
atggcactgc ctgtgacagc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cct 63

<210> 136
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 136
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagcccgc 60

cct 63

<210> 137
<211> 9
<212> PRT
<213> Homo sapiens

<400> 137
Ser Ala Arg Asn Arg Gln Lys Arg Ser
1 5

<210> 138
<211> 27
<212> DNA
<213> Homo sapiens

<400> 138
agcgccagga atcgccagaa gcggtcc 27

<210> 139
<211> 8
<212> PRT
<213> Homo sapiens

<400> 139
Ala Arg Asn Arg Gln Lys Arg Ser
1 5

<210> 140
<211> 24
<212> DNA
<213> Homo sapiens

<400> 140
gcccggaata gacagaagag atct 24

<210> 141
<211> 12
<212> PRT
<213> Homo sapiens

<400> 141
Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys
1 5 10

<210> 142
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 142
gagtctaggc gcgtgcggag aaataagcgg agcaag 36

<210> 143
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 143
gagtctcgga gagtgaggcg caataagagg agcaag 36

<210> 144
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 144
gagtccagga gagtgcggcg caacaagagg agcaag 36

<210> 145
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 145
Gly Gly Ser Gly

1

<210> 146
<211> 12
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 146
ggaggatctg ga 12

<210> 147
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 147
Gly Gly Ser Gly Gly
1 5

<210> 148
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 148
ggaggcagcg gagga 15

<210> 149
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 149
ggaggctctg gagga 15

<210> 150
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 150
ggaggctccg gcgga 15

<210> 151
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 151
ggaggatccg gaggc 15

<210> 152
<211> 15
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 152
ggaggatctg gagga 15

<210> 153
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 153
Gly Gly Ser Gly Gly Gly
1 5

<210> 154
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 154
ggtggctctg gtggtggt 18

<210> 155
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 155
ggaggtagtg gtggaggc 18

<210> 156
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 156
Gly Gly Ser Gly Gly Gly Ser Gly Gly
1 5

<210> 157
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

Linker sequence

<400> 157
ggaggtagtg gtggaggcag tggtgga 27

<210> 158
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 158
Gly Gly Gly Gly Gly
1 5

<210> 159
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 159
Gly Gly Gly Gly Ser
1 5

<210> 160
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 160
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 161
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 161
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 162
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 162
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> 163
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 163
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> 164
<211> 30
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 164
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> 165
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 165
Ser Ser Ser Ser Gly
1 5

<210> 166
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 166
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly
1 5 10

<210> 167
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 167
Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly Ser Ser Ser Ser Gly
1 5 10 15

<210> 168
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 168
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> 169
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 169
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> 170
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 170
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> 171
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 171
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> 172
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 172
tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 60

ggaggaggga gcttgcaa 78

<210> 173
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 173
gagttctcca ccgagttc 18

<210> 174
<211> 45

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 174
ggaggaggag gatccggagg aggaggatct ggcggcggcg gcagc 45

<210> 175
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 175
ggaggaggag gatccggagg aggaggatct ggcggaggag gcagc 45

<210> 176
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 176
Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
1 5 10

<210> 177
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 177
Gly Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Lys Gly
1 5 10 15

<210> 178
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 178
Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Ser Glu Gly Ser Gly Ser
1 5 10 15

Thr Lys Gly

<210> 179
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 179
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

<210> 180
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 180
Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Glu Phe
1 5 10

<210> 181
<211> 45

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 181
ggaggaggag gaagcggagg aggaggatcc ggcggaggag gctct 45

<210> 182
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 182
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> 183
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 183

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> 184
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 184
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> 185
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 185
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> 186
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 186
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> 187
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 187
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> 188
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilized Domain (DD)

<400> 188
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> 189
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 189
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> 190

<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 190
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> 191
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 191
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> 192
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 192
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> 193
<211> 1296
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 193
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgccccctc acagctgcaa ctgcctaccc tgccgctcgt catggtggcc 240

cccagcggcg caagactggg cccgttgccg cacctgcaag ccttgctgca ggaccggcca 300

catttcatgc accagctcag caccgtggac gcacatgcaa ggacacccgt gctgcaagtc 360

caccccctgg agagccctgc catgatcagc ctgacgccgc ccaccaccgc aaccggcgtg 420

ttttcactga aggcaagacc cgggctgcca ccgggcatca acgtggccag cctggaatgg 480

gtgagcaggg agccagcgct cctgtgtacc ttcccaaacc catccgcccc aagaaaggac 540

agcaccctgt ctgccgtgcc ccaatcatct tacccgctgc tggcgaatgg cgtatgcaag 600

tggcccggat gtgaaaaggt gttcgaggag ccggaagatt tcctgaaaca ttgccaggcc 660

gaccacctgt tggacgaaaa gggaagggcc caatgcctgc ttcagaggga gatggtgcag 720

agcttggagc aacaactcgt gctcgagaag gagaagctga gcgccatgca ggcacacctc 780

gccggcaaga tggccctgac caaagccagt agcgtagcca gctccgacaa gggtagctgt 840

tgcatcgtgg ccgcaggaag tcaaggcccc gttgtgcccg cctggagcgg tccaagggag 900

gcacccgact cactgttcgc cgtgaggagg catctgtggg gcagccacgg taacagcacg 960

ttccccgagt tcctgcataa catggactac ttcaagttcc acaacatgcg gcctccattc 1020

acctacgcca cactgataag gtgggctatc ctggaggctc ccgagaagca aaggaccctg 1080

aacgagatct accactggtt caccaggatg ttcgctttct ttaggaacca ccccgcgacc 1140

tggaaaaacg ccataaggca taacttgagc cttcacaagt gcttcgtgag ggtggagagt 1200

gagaaaggtg ccgtgtggac tgtggatgag ttggagttcc gcaagaagcg aagccaacga 1260

cctagcaggt gtagcaatcc aacccccgga ccctga 1296

<210> 194
<211> 1191
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 194
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgccccctc acagctgcag ctcagcaccg tggacgcaca tgcaaggaca 240

cccgtgctgc aagtccaccc cctggagagc cctgccatga tcagcctgac gccgcccacc 300

accgcaaccg gcgtgttttc actgaaggca agacccgggc tgccaccggg catcaacgtg 360

gccagcctgg aatgggtgag cagggagcca gcgctcctgt gtaccttccc aaacccatcc 420

gccccaagaa aggacagcac cctgtctgcc gtgccccaat catcttaccc gctgctggcg 480

aatggcgtat gcaagtggcc cggatgtgaa aaggtgttcg aggagccgga agatttcctg 540

aaacattgcc aggccgacca cctgttggac gaaaagggaa gggcccaatg cctgcttcag 600

agggagatgg tgcagagctt ggagcaacaa ctcgtgctcg agaaggagaa gctgagcgcc 660

atgcaggcac acctcgccgg caagatggcc ctgaccaaag ccagtagcgt agccagctcc 720

gacaagggta gctgttgcat cgtggccgca ggaagtcaag gccccgttgt gcccgcctgg 780

agcggtccaa gggaggcacc cgactcactg ttcgccgtga ggaggcatct gtggggcagc 840

cacggtaaca gcacgttccc cgagttcctg cataacatgg actacttcaa gttccacaac 900

atgcggcctc cattcaccta cgccacactg ataaggtggg ctatcctgga ggctcccgag 960

aagcaaagga ccctgaacga gatctaccac tggttcacca ggatgttcgc tttctttagg 1020

aaccaccccg cgacctggaa aaacgccata aggcataact tgagccttca caagtgcttc 1080

gtgagggtgg agagtgagaa aggtgccgtg tggactgtgg atgagttgga gttccgcaag 1140

aagcgaagcc aacgacctag caggtgtagc aatccaaccc ccggaccctg a 1191

<210> 195
<211> 1632
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 195

atgggcgtgc aggttgagac tataagccca ggcgacggca ggaccttccc caagaggggc 60

cagacatgcg tggtgcacta caccggcatg cttgaagacg gcaaaaaggt ggactcaagc 120

agggacagga acaagccctt caagttcatg ttgggcaaac aggaggtgat cagaggctgg 180

gaggagggtg ttgcccagat gagcgtgggg cagagggcca agctcacgat aagtcccgat 240

tacgcctacg gcgccaccgg tcaccccggc atcatccccc cacacgccac cctggtgttc 300

gacgtggaat tgctgaagcc cgagtcaggt ggcggtagtc cgaacccaag gccagggaag 360

ccctctgctc ctagcctggc cctcggcccc agccctggcg ctagcccctc ttggagggcg 420

gctccgaagg cttccgacct cctgggtgct aggggccctg gtggaacctt ccaaggcagg 480

gatctgcgag gaggggcgca cgcctctagc tcaagcctga acccgatgcc cccctcacag 540

ctgcaactgc ctaccctgcc gctcgtcatg gtggccccca gcggcgcaag actgggcccg 600

ttgccgcacc tgcaagcctt gctgcaggac cggccacatt tcatgcacca gctcagcacc 660

gtggacgcac atgcaaggac acccgtgctg caagtccacc ccctggagag ccctgccatg 720

atcagcctga cgccgcccac caccgcaacc ggcgtgtttt cactgaaggc aagacccggg 780

ctgccaccgg gcatcaacgt ggccagcctg gaatgggtga gcagggagcc agcgctcctg 840

tgtaccttcc caaacccatc cgccccaaga aaggacagca ccctgtctgc cgtgccccaa 900

tcatcttacc cgctgctggc gaatggcgta tgcaagtggc ccggatgtga aaaggtgttc 960

gaggagccgg aagatttcct gaaacattgc caggccgacc acctgttgga cgaaaaggga 1020

agggcccaat gcctgcttca gagggagatg gtgcagagct tggagcaaca actcgtgctc 1080

gagaaggaga agctgagcgc catgcaggca cacctcgccg gcaagatggc cctgaccaaa 1140

gccagtagcg tagccagctc cgacaagggt agctgttgca tcgtggccgc aggaagtcaa 1200

ggccccgttg tgcccgcctg gagcggtcca agggaggcac ccgactcact gttcgccgtg 1260

aggaggcatc tgtggggcag ccacggtaac agcacgttcc ccgagttcct gcataacatg 1320

gactacttca agttccacaa catgcggcct ccattcacct acgccacact gataaggtgg 1380

gctatcctgg aggctcccga gaagcaaagg accctgaacg agatctacca ctggttcacc 1440

aggatgttcg ctttctttag gaaccacccc gcgacctgga aaaacgccat aaggcataac 1500

ttgagccttc acaagtgctt cgtgagggtg gagagtgaga aaggtgccgt gtggactgtg 1560

gatgagttgg agttccgcaa gaagcgaagc caacgaccta gcaggtgtag caatccaacc 1620

cccggaccct ga 1632

<210> 196
<211> 1785
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 196
atgatctctc tgattgcggc gctggcagtt gactacgtta ttggcatgga aaacgcgatg 60

ccatggaacc tcccggctga cctggcgtgg ttcaaacgta acaccctgaa caaacctgtg 120

atcatgggtc gtcacacctg ggaatctatt ggccgtcctc tcccgggtcg taaaaacatc 180

attctgtctt ctcagccagg caccgacgac cgtgttacct gggttaaaag cgttgacgaa 240

gcgattgctg cgtgcggtga tgttcctgaa attatggtga tcggcggtgg ccgtgttatc 300

gaacagttcc tgccgaaagc gcagaaactg tacctgaccc acatcgacgc ggaagttgaa 360

ggtgacaccc acttcccgga ctacgaaccg gatgattggg agagcgtatt ctccgaattc 420

catgatgcgg atgcgcaaaa ctctcattct tactgttttg aaatcctgga acgtcgttca 480

ggtggcggta gtccgaaccc aaggccaggg aagccctctg ctcctagcct ggccctcggc 540

cccagccctg gcgctagccc ctcttggagg gcggctccga aggcttccga cctcctgggt 600

gctaggggcc ctggtggaac cttccaaggc agggatctgc gaggaggggc gcacgcctct 660

agctcaagcc tgaacccgat gccccccctca cagctgcaac tgcctaccct gccgctcgtc 720

atggtggccc ccagcggcgc aagactgggc ccgttgccgc acctgcaagc cttgctgcag 780

gaccggccac atttcatgca ccagctcagc accgtggacg cacatgcaag gacacccgtg 840

ctgcaagtcc acccccctgga gagccctgcc atgatcagcc tgacgccgcc caccaccgca 900

accggcgtgt tttcactgaa ggcaagaccc gggctgccac cgggcatcaa cgtggccagc 960

ctggaatggg tgagcaggga gccagcgctc ctgtgtacct tcccaaaccc atccgcccca 1020

agaaaggaca gcaccctgtc tgccgtgccc caatcatctt acccgctgct ggcgaatggc 1080

gtatgcaagt ggcccggatg tgaaaaggtg ttcgaggagc cggaagattt cctgaaacat 1140

tgccaggccg accacctgtt ggacgaaaag ggaagggccc aatgcctgct tcagagggag 1200

atggtgcaga gcttggagca acaactcgtg ctcgagaagg agaagctgag cgccatgcag 1260

gcacacctcg ccggcaagat ggccctgacc aaagccagta gcgtagccag ctccgacaag 1320

ggtagctgtt gcatcgtggc cgcaggaagt caaggccccg ttgtgcccgc ctggagcggt 1380

ccaagggagg cacccgactc actgttcgcc gtgaggaggc atctgtgggg cagccacggt 1440

aacagcacgt tccccgagtt cctgcataac atggactact tcaagttcca caacatgcgg 1500

cctccattca cctacgccac actgataagg tgggctatcc tggaggctcc cgagaagcaa 1560

aggaccctga acgagatcta ccactggttc accaggatgt tcgctttctt taggaaccac 1620

cccgcgacct ggaaaaacgc cataaggcat aacttgagcc ttcacaagtg cttcgtgagg 1680

gtggagagtg agaaaggtgc cgtgtggact gtggatgagt tggagttccg caagaagcga 1740

agccaacgac ctagcaggtg tagcaatcca acccccggac cctga 1785

<210> 197
<211> 1623
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 197
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgcccccctc acagctgcaa ctgcctaccc tgccgctcgt catggtggcc 240

cccagcggcg caagactggg cccgttgccg cacctgcaag ccttgctgca ggaccggcca 300

catttcatgc accagctcag caccgtggac gcacatgcaa ggacacccgt gctgcaagtc 360

caccccctgg agagccctgc catgatcagc ctgacgccgc ccaccaccgc aaccggcgtg 420

ttttcactga aggcaagacc cgggctgcca ccgggcatca acgtggccag cctggaatgg 480

gtgagcaggg agccagcgct cctgtgtacc ttcccaaacc catccgcccc aagaaaggac 540

agcaccctgt ctgccgtgcc ccaatcatct tacccgctgc tggcgaatgg cgtatgcaag 600

tggcccggat gtgaaaaggt gttcgaggag ccggaagatt tcctgaaaca ttgccaggcc 660

gaccacctgt tggacgaaaa gggaagggcc caatgcctgc ttcagaggga gatggtgcag 720

agcttggagc aacaactcgt gctcgagaag gagaagctga gcgccatgca ggcacacctc 780

gccggcaaga tggccctgac caaagccagt agcgtagcca gctccgacaa gggtagctgt 840

tgcatcgtgg ccgcaggaag tcaaggcccc gttgtgcccg cctggagcgg tccaagggag 900

gcacccgact cactgttcgc cgtgaggagg catctgtggg gcagccacgg taacagcacg 960

ttccccgagt tcctgcataa catggactac ttcaagttcc acaacatgcg gcctccattc 1020

acctacgcca cactgataag gtgggctatc ctggaggctc ccgagaagca aaggaccctg 1080

aacgagatct accactggtt caccaggatg ttcgctttct ttaggaacca ccccgcgacc 1140

tggaaaaacg ccataaggca taacttgagc cttcacaagt gcttcgtgag ggtggagagt 1200

gagaaaggtg ccgtgtggac tgtggatgag ttggagttcc gcaagaagcg aagccaacga 1260

cctagcaggt gtagcaatcc aacccccgga cccagcggcg gcgtgcaggt tgagactata 1320

agcccaggcg acggcaggac cttccccaag aggggccaga catgcgtggt gcactacacc 1380

ggcatgcttg gcgacggcaa aaaggtggac tcaagcaggg acaggaacaa gcccttcaag 1440

ttcatgttgg gcaaacagga ggtgatcaga ggctgggagg agggtgttgc ccagatgagc 1500

gtggggcagg gcgccaagct cacgataagt cccgattacg cctacggcgc caccggtcac 1560

cccggcatca tccccccaca cgccaccctg gtgttcgacg tggaattgct ggagctggag 1620

tga 1623

<210> 198
<211> 1776
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 198
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgccccctc acagctgcaa ctgcctaccc tgccgctcgt catggtggcc 240

cccagcggcg caagactggg cccgttgccg cacctgcaag ccttgctgca ggaccggcca 300

catttcatgc accagctcag caccgtggac gcacatgcaa ggacacccgt gctgcaagtc 360

caccccctgg agagccctgc catgatcagc ctgacgccgc ccaccaccgc aaccggcgtg 420

ttttcactga aggcaagacc cgggctgcca ccgggcatca acgtggccag cctggaatgg 480

gtgagcaggg agccagcgct cctgtgtacc ttcccaaacc catccgcccc aagaaaggac 540

agcaccctgt ctgccgtgcc ccaatcatct tacccgctgc tggcgaatgg cgtatgcaag 600

tggcccggat gtgaaaaggt gttcgaggag ccggaagatt tcctgaaaca ttgccaggcc 660

gaccacctgt tggacgaaaa gggaagggcc caatgcctgc ttcagaggga gatggtgcag 720

agcttggagc aacaactcgt gctcgagaag gagaagctga gcgccatgca ggcacacctc 780

gccggcaaga tggccctgac caaagccagt agcgtagcca gctccgacaa gggtagctgt 840

tgcatcgtgg ccgcaggaag tcaaggcccc gttgtgcccg cctggagcgg tccaagggag 900

gcacccgact cactgttcgc cgtgaggagg catctgtggg gcagccacgg taacagcacg 960

ttccccgagt tcctgcataa catggactac ttcaagttcc acaacatgcg gcctccattc 1020

acctacgcca cactgataag gtgggctatc ctggaggctc ccgagaagca aaggaccctg 1080

aacgagatct accactggtt caccaggatg ttcgctttct ttaggaacca ccccgcgacc 1140

tggaaaaacg ccataaggca taacttgagc cttcacaagt gcttcgtgag ggtggagagt 1200

gagaaaggtg ccgtgtggac tgtggatgag ttggagttcc gcaagaagcg aagccaacga 1260

cctagcaggt gtagcaatcc aacccccgga cccagcggca tctctctgat tgcggcgctg 1320

gcagttgact acgttattgg catggaaaac gcgatgccat ggaacctccc ggctgacctg 1380

gcgtggttca aacgtaacac cctgaacaaa cctgtgatca tgggtcgtca cacctgggaa 1440

tctattggcc gtcctctccc gggtcgtaaa aacatcattc tgtcttctca gccaggcacc 1500

gacgaccgtg ttacctgggt taaaagcgtt gacgaagcga ttgctgcgtg cggtgatgtt 1560

cctgaaatta tggtgatcgg cggtggccgt gttatcgaac agttcctgcc gaaagcgcag 1620

aaactgtacc tgacccacat cgacgcggaa gttgaaggtg acacccactt cccggactac 1680

gaaccggatg attgggagag cgtattctcc gaattccatg atgcggatgc gcaaaactct 1740

cattcttact gttttgaaat cctggaacgt cgttga 1776

<210> 199
<211> 1518
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 199
atgggcgtgc aggttgagac tataagccca ggcgacggca ggaccttccc caagaggggc 60

cagacatgcg tggtgcacta caccggcatg cttgaagacg gcaaaaaggt ggactcaagc 120

agggacagga acaagccctt caagttcatg ttgggcaaac aggaggtgat cagaggctgg 180

gaggagggtg ttgcccagat gagcgtgggg cagagggcca agctcacgat aagtcccgat 240

tacgcctacg gcgccaccgg tcaccccggc atcatccccc cacacgccac cctggtgttc 300

gacgtggaat tgctgaagcc cgagagcggc ccgaacccaa ggccagggaa gccctctgct 360

cctagcctgg ccctcggccc cagccctggc gctagcccct cttggagggc ggctccgaag 420

gcttccgacc tcctgggtgc taggggccct ggtggaacct tccaaggcag ggatctgcga 480

ggaggggcgc acgcctctag ctcaagcctg aacccgatgc ccccctcaca gctgcagctc 540

agcaccgtgg acgcacatgc aaggacaccc gtgctgcaag tccacccccc ggagagccct 600

gccatgatca gcctgacgcc gcccaccacc gcaaccggcg tgttttcact gaaggcaaga 660

cccgggctgc caccgggcat caacgtggcc agcctggaat gggtgagcag ggagccagcg 720

ctcctgtgta ccttcccaaa cccatccgcc ccaagaaagg acagcaccct gtctgccgtg 780

ccccaatcat cttacccgct gctggcgaat ggcgtatgca agtggcccgg atgtgaaaag 840

gtgttcgagg agccggaaga tttcctgaaa cattgccagg ccgaccacct gttggacgaa 900

aagggaaggg cccaatgcct gcttcagagg gagatggtgc agagcttgga gcaacaactc 960

gtgctcgaga aggagaagct gagcgccatg caggcacacc tcgccggcaa gatggccctg 1020

accaaagcca gtagcgtagc cagctccgac aagggtagct gttgcatcgt ggccgcagga 1080

agtcaaggcc ccgttgtgcc cgcctggagc ggtccaaggg aggcacccga ctcactgttc 1140

gccgtgagga ggcatctgtg gggcagccac ggtaacagca cgttccccga gttcctgcat 1200

aacatggact acttcaagtt ccacaacatg cggcctccat tcacctacgc cacactgata 1260

aggtgggcta tcctggaggc tcccgagaag caaaggaccc tgaacgagat ctaccactgg 1320

ttcaccagga tgttcgcttt ctttaggaac caccccgcga cctggaaaaa cgccataagg 1380

cataacttga gccttcacaa gtgcttcgtg agggtggaga gtgagaaagg tgccgtgtgg 1440

actgtggatg agttggagtt ccgcaagaag cgaagccaac gacctagcag gtgtagcaat 1500

ccaacccccg gaccctga 1518

<210> 200
<211> 1671
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 200
atgatctctc tgattgcggc gctggcagtt gactacgtta ttggcatgga aaacgcgatg 60

ccatggaacc tcccggctga cctggcgtgg ttcaaacgta acaccctgaa caaacctgtg 120

atcatgggtc gtcacacctg ggaatctatt ggccgtcctc tcccgggtcg taaaaacatc 180

attctgtctt ctcagccagg caccgacgac cgtgttacct gggttaaaag cgttgacgaa 240

gcgattgctg cgtgcggtga tgttcctgaa attatggtga tcggcggtgg ccgtgttatc 300

gaacagttcc tgccgaaagc gcagaaactg tacctgaccc acatcgacgc ggaagttgaa 360

ggtgacaccc acttcccgga ctacgaaccg gatgattggg agagcgtatt ctccgaattc 420

catgatgcgg atgcgcaaaa ctctcattct tactgttttg aaatcctgga acgtcgtagc 480

ggcccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 540

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 600

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 660

ctgaacccga tgcccccctc acagctgcag ctcagcaccg tggacgcaca tgcaaggaca 720

cccgtgctgc aagtccaccc cctggagagc cctgccatga tcagcctgac gccgcccacc 780

accgcaaccg gcgtgttttc actgaaggca agacccgggc tgccaccggg catcaacgtg 840

gccagcctgg aatgggtgag cagggagcca gcgctcctgt gtaccttccc aaacccatcc 900

gccccaagaa aggacagcac cctgtctgcc gtgccccaat catcttaccc gctgctggcg 960

aatggcgtat gcaagtggcc cggatgtgaa aaggtgttcg aggagccgga agatttcctg 1020

aaacattgcc aggccgacca cctgttggac gaaaagggaa gggcccaatg cctgcttcag 1080

agggagatgg tgcagagctt ggagcaacaa ctcgtgctcg agaaggagaa gctgagcgcc 1140

atgcaggcac acctcgccgg caagatggcc ctgaccaaag ccagtagcgt agccagctcc 1200

gacaagggta gctgttgcat cgtggccgca ggaagtcaag gccccgttgt gcccgcctgg 1260

agcggtccaa gggaggcacc cgactcactg ttcgccgtga ggaggcatct gtggggcagc 1320

cacggtaaca gcacgttccc cgagttcctg cataacatgg actacttcaa gttccacaac 1380

atgcggcctc cattcaccta cgccacactg ataaggtggg ctatcctgga ggctcccgag 1440

aagcaaagga ccctgaacga gatctaccac tggttcacca ggatgttcgc tttctttagg 1500

aaccaccccg cgacctggaa aaacgccata aggcataact tgagccttca caagtgcttc 1560

gtgagggtgg agagtgagaa aggtgccgtg tggactgtgg atgagttgga gttccgcaag 1620

aagcgaagcc aacgacctag caggtgtagc aatccaaccc ccggaccctg a 1671

<210> 201
<211> 1518
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 201
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgcccccctc acagctgcag ctcagcaccg tggacgcaca tgcaaggaca 240

cccgtgctgc aagtccaccc cctggagagc cctgccatga tcagcctgac gccgcccacc 300

accgcaaccg gcgtgttttc actgaaggca agacccgggc tgccaccggg catcaacgtg 360

gccagcctgg aatgggtgag cagggagcca gcgctcctgt gtaccttccc aaacccatcc 420

gccccaagaa aggacagcac cctgtctgcc gtgccccaat catcttaccc gctgctggcg 480

aatggcgtat gcaagtggcc cggatgtgaa aaggtgttcg aggagccgga agatttcctg 540

aaacattgcc aggccgacca cctgttggac gaaaagggaa gggcccaatg cctgcttcag 600

agggagatgg tgcagagctt ggagcaacaa ctcgtgctcg agaaggagaa gctgagcgcc 660

atgcaggcac acctcgccgg caagatggcc ctgaccaaag ccagtagcgt agccagctcc 720

gacaagggta gctgttgcat cgtggccgca ggaagtcaag gccccgttgt gcccgcctgg 780

agcggtccaa gggaggcacc cgactcactg ttcgccgtga ggaggcatct gtggggcagc 840

cacggtaaca gcacgttccc cgagttcctg cataacatgg actacttcaa gttccacaac 900

atgcggcctc cattcaccta cgccacactg ataaggtggg ctatcctgga ggctcccgag 960

aagcaaagga ccctgaacga gatctaccac tggttcacca ggatgttcgc tttctttagg 1020

aaccaccccg cgacctggaa aaacgccata aggcataact tgagccttca caagtgcttc 1080

gtgagggtgg agagtgagaa aggtgccgtg tggactgtgg atgagttgga gttccgcaag 1140

aagcgaagcc aacgacctag caggtgtagc aatccaaccc ccggacccag cggcggcgtg 1200

caggttgaga ctataagccc aggcgacggc aggaccttcc ccaagagggg ccagacatgc 1260

gtggtgcact acaccggcat gcttggcgac ggcaaaaagg tggactcaag cagggacagg 1320

aacaagccct tcaagttcat gttgggcaaa caggaggtga tcagaggctg ggaggagggt 1380

gttgcccaga tgagcgtggg gcagggcgcc aagctcacga taagtcccga ttacgcctac 1440

ggcgccaccg gtcaccccgg catcatcccc ccacacgcca ccctggtgtt cgacgtggaa 1500

ttgctggagc tggagtga 1518

<210> 202
<211> 1671
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 202

atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgccccccctc acagctgcag ctcagcaccg tggacgcaca tgcaaggaca 240

cccgtgctgc aagtccaccc cctggagagc cctgccatga tcagcctgac gccgcccacc 300

accgcaaccg gcgtgttttc actgaaggca agacccgggc tgccaccggg catcaacgtg 360

gccagcctgg aatgggtgag cagggagcca gcgctcctgt gtaccttccc aaacccatcc 420

gccccaagaa aggacagcac cctgtctgcc gtgccccaat catcttaccc gctgctggcg 480

aatggcgtat gcaagtggcc cggatgtgaa aaggtgttcg aggagccgga agatttcctg 540

aaacattgcc aggccgacca cctgttggac gaaaagggaa gggcccaatg cctgcttcag 600

agggagatgg tgcagagctt ggagcaacaa ctcgtgctcg agaaggagaa gctgagcgcc 660

atgcaggcac acctcgccgg caagatggcc ctgaccaaag ccagtagcgt agccagctcc 720

gacaagggta gctgttgcat cgtggccgca ggaagtcaag gccccgttgt gcccgcctgg 780

agcggtccaa gggaggcacc cgactcactg ttcgccgtga ggaggcatct gtggggcagc 840

cacggtaaca gcacgttccc cgagttcctg cataacatgg actacttcaa gttccacaac 900

atgcggcctc cattcaccta cgccacactg ataaggtggg ctatcctgga ggctcccgag 960

aagcaaagga ccctgaacga gatctaccac tggttcacca ggatgttcgc tttctttagg 1020

aaccaccccg cgacctggaa aaacgccata aggcataact tgagccttca caagtgcttc 1080

gtgagggtgg agagtgagaa aggtgccgtg tggactgtgg atgagttgga gttccgcaag 1140

aagcgaagcc aacgacctag caggtgtagc aatccaaccc ccggacccag cggcatctct 1200

ctgattgcgg cgctggcagt tgactacgtt attggcatgg aaaacgcgat gccatggaac 1260

ctcccggctg acctggcgtg gttcaaacgt aacaccctga acaaacctgt gatcatgggt 1320

cgtcacacct gggaatctat tggccgtcct ctcccgggtc gtaaaaacat cattctgtct 1380

tctcagccag gcaccgacga ccgtgttacc tgggttaaaa gcgttgacga agcgattgct 1440

gcgtgcggtg atgttcctga aattatggtg atcggcggtg gccgtgttat cgaacagttc 1500

ctgccgaaag cgcagaaact gtacctgacc cacatcgacg cggaagttga aggtgacacc 1560

cacttcccgg actacgaacc ggatgattgg gagagcgtat tctccgaatt ccatgatgcg 1620

gatgcgcaaa actctcattc ttactgtttt gaaatcctgg aacgtcgttg a 1671

<210> 203
<211> 936
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 203
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> 204
<211> 1983
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 204
atgggcgtgc aggttgagac tataagccca ggcgacggca ggaccttccc caagaggggc 60

cagacatgcg tggtgcacta caccggcatg cttgaagacg gcaaaaaggt ggactcaagc 120

agggacagga acaagccctt caagttcatg ttgggcaaac aggaggtgat cagaggctgg 180

gaggagggtg ttgcccagat gagcgtgggg cagagggcca agctcacgat aagtcccgat 240

tacgcctacg gcgccaccgg tcaccccggc atcatccccc cacacgccac cctggtgttc 300

gacgtggaat tgctgaagcc cgaggagttc atggaagatg ccaaaaacat taagaagggc 360

ccagcgccat tctacccact cgaagacggg accgccggcg agcagctgca caaagccatg 420

aagcgctacg ccctggtgcc cggcaccatc gcctttaccg acgcacatat cgaggtggac 480

attacctacg ccgagtactt cgagatgagc gttcggctgg cagaagctat gaagcgctat 540

gggctgaata caaaccatcg gatcgtggtg tgcagcgaga atagcttgca gttcttcatg 600

cccgtgttgg gtgccctgtt catcggtgtg gctgtggccc cagctaacga catctacaac 660

gagcgcgagc tgctgaacag catgggcatc agccagccca ccgtcgtatt cgtgagcaag 720

aaagggctgc aaaagatcct caacgtgcaa aagaagctac cgatcataca aaagatcatc 780

atcatggata gcaagaccga ctaccagggc ttccaaagca tgtacacctt cgtgacttcc 840

catttgccac ccggcttcaa cgagtacgac ttcgtgcccg agagcttcga ccgggacaaa 900

accatcgccc tgatcatgaa cagtagtggc agtaccggat tgcccaaggg cgtagcccta 960

ccgcaccgca ccgcttgtgt ccgattcagt catgcccgcg accccatctt cggcaaccag 1020

atcatccccg acaccgctat cctcagcgtg gtgccatttc accacggctt cggcatgttc 1080

accacgctgg gctacttgat ctgcggcttt cgggtcgtgc tcatgtaccg cttcgaggag 1140

gagctattct tgcgcagctt gcaagactat aagattcaat ctgccctgct ggtgcccaca 1200

ctatttagct tcttcgctaa gagcactctc atcgacaagt acgacctaag caacttgcac 1260

gagatcgcca gcggcggggc gccgctcagc aaggaggtag gtgaggccgt ggccaaacgc 1320

ttccacctac caggcatccg ccagggctac ggcctgacag aaacaaccag cgccattctg 1380

atcacccccg aaggggacga caagcctggc gcagtaggca aggtggtgcc cttcttcgag 1440

gctaaggtgg tggacttgga caccggtaag acactgggtg tgaaccagcg cggcgagctg 1500

tgcgtccgtg gccccatgat catgagcggc tacgttaaca accccgaggc tacaaacgct 1560

ctcatcgaca aggacggctg gctgcacagc ggcgacatcg cctactggga cgaggacgag 1620

cacttcttca tcgtggaccg gctgaagagc ctgatcaaat acaagggcta ccaggtagcc 1680

ccagccgaac tggagagcat cctgctgcaa caccccaaca tcttcgacgc cggggtcgcc 1740

ggcctgcccg acgacgatgc cggcgagctg cccgccgcag tcgtcgtgct ggaacacggt 1800

aaaaccatga ccgagaagga gatcgtggac tatgtggcca gccaggttac aaccgccaag 1860

aagctgcgcg gtggtgttgt gttcgtggac gaggtgccta aaggactgac cggcaagttg 1920

gacgcccgca agatccgcga gattctcatt aaggccaaga agggcggcaa gagcaagctg 1980

tga 1983

<210> 205
<211> 1263
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 205
atgggcgtgc aggttgagac tataagccca ggcgacggca ggaccttccc caagaggggc 60

cagacatgcg tggtgcacta caccggcatg cttgaagacg gcaaaaaggt ggactcaagc 120

agggacagga acaagccctt caagttcatg ttgggcaaac aggaggtgat cagaggctgg 180

gaggagggtg ttgcccagat gagcgtgggg cagagggcca agctcacgat aagtcccgat 240

tacgcctacg gcgccaccgg tcaccccggc atcatccccc cacacgccac cctggtgttc 300

gacgtggaat tgctgaagcc cgagagcggc acttccaagg tgtacgaccc cgagcaacgc 360

aaacgcatga tcactgggcc tcagtggtgg gctcgctgca agcaaatgaa cgtgctggac 420

tccttcatca actactatga ttccgagaag cacgccgaga acgccgtgat ttttctgcat 480

ggtaacgctg cctccagcta cctgtggagg cacgtcgtgc ctcacatcga gcccgtggct 540

agatgcatca tccctgatct gatcggaatg ggtaagtccg gcaagagcgg gaatggctca 600

tatcgcctcc tggatcacta caagtacctc accgcttggt tcgagctgct gaaccttcca 660

aagaaaatca tctttgtggg ccacgactgg ggggcttgtc tggcctttca ctactcctac 720

gagcaccaag acaagatcaa ggccatcgtc catgctgaga gtgtcgtgga cgtgatcgag 780

tcctgggacg agtggcctga catcgaggag gatatcgccc tgatcaagag cgaagagggc 840

gagaaaatgg tgcttgagaa taacttcttc gtcgagacca tgctcccaag caagatcatg 900

cggaaactgg agcctgagga gttcgctgcc tacctggagc cattcaagga gaagggcgag 960

gttagacggc ctaccctctc ctggcctcgc gagatccctc tcgttaaggg aggcaagccc 1020

gacgtcgtcc agattgtccg caactacaac gcctaccttc gggccagcga cgatctgcct 1080

aagatgttca tcgagtccga ccctgggttc ttttccaacg ctattgtcga gggagctaag 1140

aagttcccta acaccgagtt cgtgaaggtg aagggcctcc acttcagcca ggaggacgct 1200

ccagatgaaa tgggtaagta catcaagagc ttcgtggagc gcgtgctgaa gaacgagcag 1260

taa 1263

<210> 206
<211> 1416
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 206
atgatctctc tgattgcggc gctggcagtt gactacgtta ttggcatgga aaacgcgatg 60

ccatggaacc tcccggctga cctggcgtgg ttcaaacgta acaccctgaa caaacctgtg 120

atcatgggtc gtcacacctg ggaatctatt ggccgtcctc tcccgggtcg taaaaacatc 180

attctgtctt ctcagccagg caccgacgac cgtgttacct gggttaaaag cgttgacgaa 240

gcgattgctg cgtgcggtga tgttcctgaa attatggtga tcggcggtgg ccgtgttatc 300

gaacagttcc tgccgaaagc gcagaaactg tacctgaccc acatcgacgc ggaagttgaa 360

ggtgacaccc acttcccgga ctacgaaccg gatgattggg agagcgtatt ctccgaattc 420

catgatgcgg atgcgcaaaa ctctcattct tactgttttg aaatcctgga acgtcgtagc 480

ggcacttcca aggtgtacga ccccgagcaa cgcaaacgca tgatcactgg gcctcagtgg 540

tgggctcgct gcaagcaaat gaacgtgctg gactccttca tcaactacta tgattccgag 600

aagcacgccg agaacgccgt gatttttctg catggtaacg ctgcctccag ctacctgtgg 660

aggcacgtcg tgcctcacat cgagcccgtg gctagatgca tcatccctga tctgatcgga 720

atgggtaagt ccggcaagag cgggaatggc tcatatcgcc tcctggatca ctacaagtac 780

ctcaccgctt ggttcgagct gctgaacctt ccaaagaaaa tcatctttgt gggccacgac 840

tgggggggctt gtctggcctt tcactactcc tacgagcacc aagacaagat caaggccatc 900

gtccatgctg agagtgtcgt ggacgtgatc gagtcctggg acgagtggcc tgacatcgag 960

gaggatatcg ccctgatcaa gagcgaagag ggcgagaaaa tggtgcttga gaataacttc 1020

ttcgtcgaga ccatgctccc aagcaagatc atgcggaaac tggagcctga ggagttcgct 1080

gcctacctgg agccattcaa ggagaagggc gaggttagac ggcctaccct ctcctggcct 1140

cgcgagatcc ctctcgttaa gggaggcaag cccgacgtcg tccagattgt ccgcaactac 1200

aacgcctacc ttcgggccag cgacgatctg cctaagatgt tcatcgagtc cgaccctggg 1260

ttcttttcca acgctattgt cgagggagct aagaagttcc ctaacaccga gttcgtgaag 1320

gtgaagggcc tccacttcag ccaggaggac gctccagatg aaatgggtaa gtacatcaag 1380

agcttcgtgg agcgcgtgct gaagaacgag cagtaa 1416

<210> 207
<211> 1263
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 207
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 cagagcggcg gcgtgcaggt tgagactata 960

agcccaggcg acggcaggac cttccccaag aggggccaga catgcgtggt gcactacacc 1020

ggcatgcttg gcgacggcaa aaaggtggac tcaagcaggg acaggaacaa gcccttcaag 1080

ttcatgttgg gcaaacagga ggtgatcaga ggctgggagg agggtgttgc ccagatgagc 1140

gtggggcagg gcgccaagct cacgataagt cccgattacg cctacggcgc caccggtcac 1200

cccggcatca tccccccaca cgccaccctg gtgttcgacg tggaattgct ggagctggag 1260

tga 1263

<210> 208
<211> 1416
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 208
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 cagagcggca tctctctgat tgcggcgctg 960

gcagttgact acgttattgg catggaaaac gcgatgccat ggaacctccc ggctgacctg 1020

gcgtggttca aacgtaacac cctgaacaaa cctgtgatca tgggtcgtca cacctgggaa 1080

tctattggcc gtcctctccc gggtcgtaaa aacatcattc tgtcttctca gccaggcacc 1140

gacgaccgtg ttacctgggt taaaagcgtt gacgaagcga ttgctgcgtg cggtgatgtt 1200

cctgaaatta tggtgatcgg cggtggccgt gttatcgaac agttcctgcc gaaagcgcag 1260

aaactgtacc tgacccacat cgacgcggaa gttgaaggtg acacccactt cccggactac 1320

gaaccggatg attgggagag cgtattctcc gaattccatg atgcggatgc gcaaaactct 1380

cattcttact gttttgaaat cctggaacgt cgttga 1416

<210> 209
<211> 311
<212> PRT
<213> Renilla reniformis

<400> 209
Met Thr Ser Lys Val Tyr Asp Pro Glu Gln Arg Lys Arg Met Ile Thr
1 5 10 15

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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
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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> 210
<211> 550
<212> PRT
<213> Photinus pyralis

<400> 210
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
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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> 211
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 211
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> 212
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 212
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 Glu Phe Met Glu
100 105 110

Asp Ala Lys Asn Ile Lys Lys Gly Pro Ala Pro Phe Tyr Pro Leu Glu
115 120 125

Asp Gly Thr Ala Gly Glu Gln Leu His Lys Ala Met Lys Arg Tyr Ala
130 135 140

Leu Val Pro Gly Thr Ile Ala Phe Thr Asp Ala His Ile Glu Val Asp
145 150 155 160

```
Ile Thr Tyr Ala Glu Tyr Phe Glu Met Ser Val Arg Leu Ala Glu Ala
                165                 170                 175

Met Lys Arg Tyr Gly Leu Asn Thr Asn His Arg Ile Val Val Cys Ser
            180                 185                 190

Glu Asn Ser Leu Gln Phe Phe Met Pro Val Leu Gly Ala Leu Phe Ile
        195                 200                 205

Gly Val Ala Val Ala Pro Ala Asn Asp Ile Tyr Asn Glu Arg Glu Leu
    210                 215                 220

Leu Asn Ser Met Gly Ile Ser Gln Pro Thr Val Val Phe Val Ser Lys
225                 230                 235                 240

Lys Gly Leu Gln Lys Ile Leu Asn Val Gln Lys Lys Leu Pro Ile Ile
                245                 250                 255

Gln Lys Ile Ile Ile Met Asp Ser Lys Thr Asp Tyr Gln Gly Phe Gln
            260                 265                 270

Ser Met Tyr Thr Phe Val Thr Ser His Leu Pro Pro Gly Phe Asn Glu
        275                 280                 285

Tyr Asp Phe Val Pro Glu Ser Phe Asp Arg Asp Lys Thr Ile Ala Leu
    290                 295                 300

Ile Met Asn Ser Ser Gly Ser Thr Gly Leu Pro Lys Gly Val Ala Leu
305                 310                 315                 320

Pro His Arg Thr Ala Cys Val Arg Phe Ser His Ala Arg Asp Pro Ile
                325                 330                 335

Phe Gly Asn Gln Ile Ile Pro Asp Thr Ala Ile Leu Ser Val Val Pro
            340                 345                 350

Phe His His Gly Phe Gly Met Phe Thr Thr Leu Gly Tyr Leu Ile Cys
        355                 360                 365
```

```
Gly Phe Arg Val Val Leu Met Tyr Arg Phe Glu Glu Glu Leu Phe Leu
    370                 375                 380

Arg Ser Leu Gln Asp Tyr Lys Ile Gln Ser Ala Leu Leu Val Pro Thr
385                 390                 395                 400

Leu Phe Ser Phe Phe Ala Lys Ser Thr Leu Ile Asp Lys Tyr Asp Leu
                405                 410                 415

Ser Asn Leu His Glu Ile Ala Ser Gly Gly Ala Pro Leu Ser Lys Glu
            420                 425                 430

Val Gly Glu Ala Val Ala Lys Arg Phe His Leu Pro Gly Ile Arg Gln
        435                 440                 445

Gly Tyr Gly Leu Thr Glu Thr Thr Ser Ala Ile Leu Ile Thr Pro Glu
    450                 455                 460

Gly Asp Asp Lys Pro Gly Ala Val Gly Lys Val Val Pro Phe Phe Glu
465                 470                 475                 480

Ala Lys Val Val Asp Leu Asp Thr Gly Lys Thr Leu Gly Val Asn Gln
                485                 490                 495

Arg Gly Glu Leu Cys Val Arg Gly Pro Met Ile Met Ser Gly Tyr Val
            500                 505                 510

Asn Asn Pro Glu Ala Thr Asn Ala Leu Ile Asp Lys Asp Gly Trp Leu
        515                 520                 525

His Ser Gly Asp Ile Ala Tyr Trp Asp Glu Asp Glu His Phe Phe Ile
    530                 535                 540

Val Asp Arg Leu Lys Ser Leu Ile Lys Tyr Lys Gly Tyr Gln Val Ala
545                 550                 555                 560

Pro Ala Glu Leu Glu Ser Ile Leu Leu Gln His Pro Asn Ile Phe Asp
                565                 570                 575
```

Ala Gly Val Ala Gly Leu Pro Asp Asp Asp Ala Gly Glu Leu Pro Ala
580 585 590

Ala Val Val Val Leu Glu His Gly Lys Thr Met Thr Glu Lys Glu Ile
595 600 605

Val Asp Tyr Val Ala Ser Gln Val Thr Thr Ala Lys Lys Leu Arg Gly
610 615 620

Gly Val Val Phe Val Asp Glu Val Pro Lys Gly Leu Thr Gly Lys Leu
625 630 635 640

Asp Ala Arg Lys Ile Arg Glu Ile Leu Ile Lys Ala Lys Lys Gly Gly
645 650 655

Lys Ser Lys Leu
660

<210> 213
<211> 420
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 213
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 Ser Gly Thr Ser
            100                 105                 110

Lys Val Tyr Asp Pro Glu Gln Arg Lys Arg Met Ile Thr Gly Pro Gln
        115                 120                 125

Trp Trp Ala Arg Cys Lys Gln Met Asn Val Leu Asp Ser Phe Ile Asn
    130                 135                 140

Tyr Tyr Asp Ser Glu Lys His Ala Glu Asn Ala Val Ile Phe Leu His
145                 150                 155                 160

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

Glu Pro Val Ala Arg Cys Ile Ile Pro Asp Leu Ile Gly Met Gly Lys
            180                 185                 190

Ser Gly Lys Ser Gly Asn Gly Ser Tyr Arg Leu Leu Asp His Tyr Lys
        195                 200                 205

Tyr Leu Thr Ala Trp Phe Glu Leu Leu Asn Leu Pro Lys Lys Ile Ile
    210                 215                 220

Phe Val Gly His Asp Trp Gly Ala Cys Leu Ala Phe His Tyr Ser Tyr
225                 230                 235                 240

Glu His Gln Asp Lys Ile Lys Ala Ile Val His Ala Glu Ser Val Val
                245                 250                 255

Asp Val Ile Glu Ser Trp Asp Glu Trp Pro Asp Ile Glu Glu Asp Ile
            260                 265                 270

Ala Leu Ile Lys Ser Glu Glu Gly Glu Lys Met Val Leu Glu Asn Asn
        275                 280                 285
```

```
Phe Phe Val Glu Thr Met Leu Pro Ser Lys Ile Met Arg Lys Leu Glu
    290                 295                 300

Pro Glu Glu Phe Ala Ala Tyr Leu Glu Pro Phe Lys Glu Lys Gly Glu
305                 310                 315                 320

Val Arg Arg Pro Thr Leu Ser Trp Pro Arg Glu Ile Pro Leu Val Lys
                325                 330                 335

Gly Gly Lys Pro Asp Val Val Gln Ile Val Arg Asn Tyr Asn Ala Tyr
            340                 345                 350

Leu Arg Ala Ser Asp Asp Leu Pro Lys Met Phe Ile Glu Ser Asp Pro
        355                 360                 365

Gly Phe Phe Ser Asn Ala Ile Val Glu Gly Ala Lys Lys Phe Pro Asn
    370                 375                 380

Thr Glu Phe Val Lys Val Lys Gly Leu His Phe Ser Gln Glu Asp Ala
385                 390                 395                 400

Pro Asp Glu Met Gly Lys Tyr Ile Lys Ser Phe Val Glu Arg Val Leu
                405                 410                 415

Lys Asn Glu Gln
            420
```

<210> 214
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 214

```
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 Ser
145                 150                 155                 160

Gly Thr Ser Lys Val Tyr Asp Pro Glu Gln Arg Lys Arg Met Ile Thr
                165                 170                 175

Gly Pro Gln Trp Trp Ala Arg Cys Lys Gln Met Asn Val Leu Asp Ser
            180                 185                 190

Phe Ile Asn Tyr Tyr Asp Ser Glu Lys His Ala Glu Asn Ala Val Ile
        195                 200                 205

Phe Leu His Gly Asn Ala Ala Ser Ser Tyr Leu Trp Arg His Val Val
    210                 215                 220
```

```
Pro His Ile Glu Pro Val Ala Arg Cys Ile Ile Pro Asp Leu Ile Gly
225                 230                 235                 240

Met Gly Lys Ser Gly Lys Ser Gly Asn Gly Ser Tyr Arg Leu Leu Asp
                245                 250                 255

His Tyr Lys Tyr Leu Thr Ala Trp Phe Glu Leu Leu Asn Leu Pro Lys
            260                 265                 270

Lys Ile Ile Phe Val Gly His Asp Trp Gly Ala Cys Leu Ala Phe His
        275                 280                 285

Tyr Ser Tyr Glu His Gln Asp Lys Ile Lys Ala Ile Val His Ala Glu
    290                 295                 300

Ser Val Val Asp Val Ile Glu Ser Trp Asp Glu Trp Pro Asp Ile Glu
305                 310                 315                 320

Glu Asp Ile Ala Leu Ile Lys Ser Glu Glu Gly Glu Lys Met Val Leu
                325                 330                 335

Glu Asn Asn Phe Phe Val Glu Thr Met Leu Pro Ser Lys Ile Met Arg
            340                 345                 350

Lys Leu Glu Pro Glu Glu Phe Ala Ala Tyr Leu Glu Pro Phe Lys Glu
        355                 360                 365

Lys Gly Glu Val Arg Arg Pro Thr Leu Ser Trp Pro Arg Glu Ile Pro
    370                 375                 380

Leu Val Lys Gly Gly Lys Pro Asp Val Val Gln Ile Val Arg Asn Tyr
385                 390                 395                 400

Asn Ala Tyr Leu Arg Ala Ser Asp Asp Leu Pro Lys Met Phe Ile Glu
                405                 410                 415

Ser Asp Pro Gly Phe Phe Ser Asn Ala Ile Val Glu Gly Ala Lys Lys
            420                 425                 430
```

Phe Pro Asn Thr Glu Phe Val Lys Val Lys Gly Leu His Phe Ser Gln
435 440 445

Glu Asp Ala Pro Asp Glu Met Gly Lys Tyr Ile Lys Ser Phe Val Glu
450 455 460

Arg Val Leu Lys Asn Glu Gln
465 470

<210> 215
<211> 420
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 215
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 Ser Gly Gly Val Gln Val Glu Thr Ile
305                 310                 315                 320

Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val
                325                 330                 335
```

Val His Tyr Thr Gly Met Leu Gly Asp Gly Lys Lys Val Asp Ser Ser
340 345 350

Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val
355 360 365

Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Gly
370 375 380

Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His
385 390 395 400

Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu
405 410 415

Leu Glu Leu Glu
420

<210> 216
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 216
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 Ser Gly Ile Ser Leu Ile Ala Ala Leu
305                 310                 315                 320

Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala Met Pro Trp Asn Leu
                325                 330                 335

Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn Lys Pro Val
            340                 345                 350

Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro Leu Pro Gly
        355                 360                 365

Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp Asp Arg Val
    370                 375                 380

Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys Gly Asp Val
385                 390                 395                 400

Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Ile Glu Gln Phe Leu
                405                 410                 415

Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala Glu Val Glu
            420                 425                 430

Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp Asp Trp Glu Ser Val
        435                 440                 445

Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser His Ser Tyr Cys
    450                 455                 460

Phe Glu Ile Leu Glu Arg Arg
465                 470
```

<210> 217
<211> 936
<212> DNA
<213> Renilla reniformis

<400> 217
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> 218
<211> 1653
<212> DNA
<213> Photinus pyralis

<400> 218
atggaagatg ccaaaaacat taagaagggc ccagcgccat tctacccact cgaagacggg 60

accgccggcg agcagctgca caaagccatg aagcgctacg ccctggtgcc cggcaccatc 120

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> 219
<211> 45

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 219
ggaggaggag gcagcggagg aggaggttct ggaggaggcg gcagc 45

<210> 220
<211> 603
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Promoter sequence

<400> 220
aagcttggga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 60

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaatagga 120

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 180

aagtgtatca tatgccaagt acgccccta 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> 221
<211> 399
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Promoter sequence

<400> 221
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> 222
<211> 1339
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Promoter sequence

<400> 222
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 gttcttttc 360

gcaacgggtt tgccgccaga acacaggtaa gtgccgtgtg tggttcccgc gggcctggcc 420

tctttacggg ttatggccct tgcgtgcctt gaattacttc cacgccctg 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> 223
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 223
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> 224
<211> 766
<212> PRT
<213> Homo sapiens

<400> 224

```
Met Lys Thr Pro Trp Lys Val Leu Leu Gly Leu Leu Gly Ala Ala Ala
1               5                   10                  15

Leu Val Thr Ile Ile Thr Val Pro Val Val Leu Leu Asn Lys Gly Thr
            20                  25                  30
```

```
Asp Asp Ala Thr Ala Asp Ser Arg Lys Thr Tyr Thr Leu Thr Asp Tyr
        35                  40                  45

Leu Lys Asn Thr Tyr Arg Leu Lys Leu Tyr Ser Leu Arg Trp Ile Ser
    50                  55                  60

Asp His Glu Tyr Leu Tyr Lys Gln Glu Asn Asn Ile Leu Val Phe Asn
65                  70                  75                  80

Ala Glu Tyr Gly Asn Ser Ser Val Phe Leu Glu Asn Ser Thr Phe Asp
                85                  90                  95

Glu Phe Gly His Ser Ile Asn Asp Tyr Ser Ile Ser Pro Asp Gly Gln
            100                 105                 110

Phe Ile Leu Leu Glu Tyr Asn Tyr Val Lys Gln Trp Arg His Ser Tyr
        115                 120                 125

Thr Ala Ser Tyr Asp Ile Tyr Asp Leu Asn Lys Arg Gln Leu Ile Thr
    130                 135                 140

Glu Glu Arg Ile Pro Asn Asn Thr Gln Trp Val Thr Trp Ser Pro Val
145                 150                 155                 160

Gly His Lys Leu Ala Tyr Val Trp Asn Asn Asp Ile Tyr Val Lys Ile
                165                 170                 175

Glu Pro Asn Leu Pro Ser Tyr Arg Ile Thr Trp Thr Gly Lys Glu Asp
            180                 185                 190

Ile Ile Tyr Asn Gly Ile Thr Asp Trp Val Tyr Glu Glu Glu Val Phe
        195                 200                 205

Ser Ala Tyr Ser Ala Leu Trp Trp Ser Pro Asn Gly Thr Phe Leu Ala
    210                 215                 220

Tyr Ala Gln Phe Asn Asp Thr Glu Val Pro Leu Ile Glu Tyr Ser Phe
225                 230                 235                 240
```

```
Tyr Ser Asp Glu Ser Leu Gln Tyr Pro Lys Thr Val Arg Val Pro Tyr
                245                 250                 255

Pro Lys Ala Gly Ala Val Asn Pro Thr Val Lys Phe Phe Val Val Asn
            260                 265                 270

Thr Asp Ser Leu Ser Ser Val Thr Asn Ala Thr Ser Ile Gln Ile Thr
        275                 280                 285

Ala Pro Ala Ser Met Leu Ile Gly Asp His Tyr Leu Cys Asp Val Thr
    290                 295                 300

Trp Ala Thr Gln Glu Arg Ile Ser Leu Gln Trp Leu Arg Arg Ile Gln
305                 310                 315                 320

Asn Tyr Ser Val Met Asp Ile Cys Asp Tyr Asp Glu Ser Ser Gly Arg
                325                 330                 335

Trp Asn Cys Leu Val Ala Arg Gln His Ile Glu Met Ser Thr Thr Gly
            340                 345                 350

Trp Val Gly Arg Phe Arg Pro Ser Glu Pro His Phe Thr Leu Asp Gly
        355                 360                 365

Asn Ser Phe Tyr Lys Ile Ile Ser Asn Glu Glu Gly Tyr Arg His Ile
    370                 375                 380

Cys Tyr Phe Gln Ile Asp Lys Lys Asp Cys Thr Phe Ile Thr Lys Gly
385                 390                 395                 400

Thr Trp Glu Val Ile Gly Ile Glu Ala Leu Thr Ser Asp Tyr Leu Tyr
                405                 410                 415

Tyr Ile Ser Asn Glu Tyr Lys Gly Met Pro Gly Gly Arg Asn Leu Tyr
            420                 425                 430

Lys Ile Gln Leu Ser Asp Tyr Thr Lys Val Thr Cys Leu Ser Cys Glu
        435                 440                 445
```

```
Leu Asn Pro Glu Arg Cys Gln Tyr Tyr Ser Val Ser Phe Ser Lys Glu
    450                 455                 460

Ala Lys Tyr Tyr Gln Leu Arg Cys Ser Gly Pro Gly Leu Pro Leu Tyr
465                 470                 475                 480

Thr Leu His Ser Ser Val Asn Asp Lys Gly Leu Arg Val Leu Glu Asp
                485                 490                 495

Asn Ser Ala Leu Asp Lys Met Leu Gln Asn Val Gln Met Pro Ser Lys
            500                 505                 510

Lys Leu Asp Phe Ile Ile Leu Asn Glu Thr Lys Phe Trp Tyr Gln Met
        515                 520                 525

Ile Leu Pro Pro His Phe Asp Lys Ser Lys Lys Tyr Pro Leu Leu Leu
    530                 535                 540

Asp Val Tyr Ala Gly Pro Cys Ser Gln Lys Ala Asp Thr Val Phe Arg
545                 550                 555                 560

Leu Asn Trp Ala Thr Tyr Leu Ala Ser Thr Glu Asn Ile Ile Val Ala
                565                 570                 575

Ser Phe Asp Gly Arg Gly Ser Gly Tyr Gln Gly Asp Lys Ile Met His
            580                 585                 590

Ala Ile Asn Arg Arg Leu Gly Thr Phe Glu Val Glu Asp Gln Ile Glu
        595                 600                 605

Ala Ala Arg Gln Phe Ser Lys Met Gly Phe Val Asp Asn Lys Arg Ile
    610                 615                 620

Ala Ile Trp Gly Trp Ser Tyr Gly Gly Tyr Val Thr Ser Met Val Leu
625                 630                 635                 640

Gly Ser Gly Ser Gly Val Phe Lys Cys Gly Ile Ala Val Ala Pro Val
                645                 650                 655
```

Ser Arg Trp Glu Tyr Tyr Asp Ser Val Tyr Thr Glu Arg Tyr Met Gly
660 665 670

Leu Pro Thr Pro Glu Asp Asn Leu Asp His Tyr Arg Asn Ser Thr Val
675 680 685

Met Ser Arg Ala Glu Asn Phe Lys Gln Val Glu Tyr Leu Leu Ile His
690 695 700

Gly Thr Ala Asp Asp Asn Val His Phe Gln Gln Ser Ala Gln Ile Ser
705 710 715 720

Lys Ala Leu Val Asp Val Gly Val Asp Phe Gln Ala Met Trp Tyr Thr
725 730 735

Asp Glu Asp His Gly Ile Ala Ser Ser Thr Ala His Gln His Ile Tyr
740 745 750

Thr His Met Ser His Phe Ile Lys Gln Cys Phe Ser Leu Pro
755 760 765

<210> 225
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 225
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> 226
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 226
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> 227
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 227

```
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> 228
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 228

```
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> 229
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 229
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> 230
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Destabilizing Domain (DD)

<400> 230
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> 231
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 231
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> 232
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 232
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> 233
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 233
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> 234
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 234
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> 235
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 235
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> 236
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 236
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> 237
<211> 186

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 237

```
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> 238
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Destabilizing Domain (DD)

<400> 238
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> 239
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Destabilizing Domain (DD)

<400> 239
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> 240
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 240
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> 241
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 241
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
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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> 242
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 242
Asp Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn Tyr Asn Ser Ala Leu Lys
50 55 60

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

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

Arg Glu His Tyr Tyr Gly Ser Ser Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Ala Ser Ile Thr Val Ser Ser
115

<210> 243
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 243
Asp Val Gln Leu Gln Glu Ser Gly Pro Val Leu Val Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Thr Ala Ser Gly Tyr Thr Phe Thr Asp His
20 25 30

Phe Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg His Asn Trp Gly Ala Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 244
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 244
Asp Val Gln Leu Gln Glu Ser Gly Pro Val Leu Val Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Thr Ala Ser Gly Tyr Thr Phe Thr Asp His
20 25 30

Phe Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg His Asn Trp Gly Ala Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 245
<211> 120

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 245
Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

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

Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 246
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 246
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 Phe Ser Leu Thr Ser Tyr
            20                  25                  30


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


Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met Asp Tyr Trp Trp Gly
            100                 105                 110


Gln Gly Thr Met Val Thr Val
        115


<210> 247
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 247
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


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

Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr Phe Asp Tyr Trp Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val
115

<210> 248
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 248
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 Thr Phe Thr Asp His
20 25 30

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

Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg His Asn Trp Gly Ala Tyr Phe Asp Tyr Trp Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val
115

<210> 249
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 249
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 Thr Phe Thr Asp Tyr
20 25 30

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

Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser Phe Asp Tyr Trp Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val
115

<210> 250
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 250
Gly Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Tyr Gly Asn Thr Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

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

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

<210> 251
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 251
Asp Val Gln Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

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

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50   55   60

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

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

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

<210> 252
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 252
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1   5   10   15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His 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 Arg Leu Ile Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro
    50   55   60

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

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

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

<210> 253
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 253
Asp Val Gln Met Ile Gln Thr Pro 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 Gly Asn Tyr
20 25 30

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

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

Ser Gly Ser Gly Thr Glu 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 Ser Ala Leu Pro Pro
85 90 95

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

<210> 254
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 254
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Gly Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

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

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

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His
85 90 95

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

<210> 255
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 255
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

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

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

<210> 256
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 256
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg
50 55 60

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

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu
85 90 95

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

<210> 257
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 257
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr
20 25 30

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

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

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

Phe Ala Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe
85 90 95

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

<210> 258
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 258
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 259
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 259
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 Asn Tyr
20 25 30

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

Tyr Tyr Thr Ser Ile 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 Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
85 90 95

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

<210> 260
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 260
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 261
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 261
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile Tyr
            20   25   30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35   40   45

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

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

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

Arg His Ser Gly Tyr Gly Thr His Trp Gly Val Leu Phe Ala Tyr Trp
            100   105   110

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

<210> 262
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 262
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

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

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

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

Arg His Ser Gly Tyr Gly Ser Ser Tyr Gly Val Leu Phe Ala Tyr Trp
100 105 110

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

<210> 263
<211> 120
<212> PRT
<213> Mus musculus

<400> 263
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Tyr Ile Ser Ser Asp Ser Ser Ala Ile Tyr Tyr Ala Asp Thr 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 Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Gly Arg Gly Arg Glu Asn Ile Tyr Tyr Gly Ser Arg Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val
115 120

<210> 264
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 264
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 Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

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

Thr Met Val Thr Val Ser Ser
115

<210> 265
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 265
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 Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 266
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 266
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
            20   25   30

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

Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

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

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

Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100   105   110

Val Thr Val Ser Ser
        115

<210> 267
<211> 107
<212> PRT
<213> Mus musculus

<400> 267

Asp 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 Lys Ala Ser Gln Asn Val Asp Thr Asn
20 25 30

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

Tyr Ser Ala Ser Tyr Arg Tyr 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 Tyr Asn Asn Tyr Pro Phe
85 90 95

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

<210> 268
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 268
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser 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 Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95


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


<210> 269
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 269
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


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


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


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


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


Pro Thr Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 270
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 270
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Gly 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 Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Pro
85 90 95

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

<210> 271
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 271
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60

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

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

Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220
```

```
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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> 272
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 272
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

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

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

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

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

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

Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val
100 105 110

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
115 120 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
130 135 140

```
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145                 150                 155                 160


Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175


Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190


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


Gly Glu Cys
    210


<210> 273
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 273
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15


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


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


Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60


Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80
```

```
Lys Met Asn Ser Leu Gln Ile Asp Asp Thr Ala Met Tyr Tyr Cys Ala
                85                  90                  95

Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285
```

```
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445
```

<210> 274
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 274

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

```
Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ser Val Thr Asn Tyr
            20                  25                  30

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60

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

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

Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220
```

```
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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

<210> 275
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 275
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1   5   10   15

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

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

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

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65   70   75   80

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

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
        115   120   125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
    130   135   140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145 150 155 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
165 170 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
180 185 190

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

Gly Glu Cys
210

<210> 276
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 276
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Val Val Gln Pro Gly Gln
1 5 10 15

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
50 55 60

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

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

```
Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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


<210> 277
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 277
Ser Ile Val Met Thr Gln Thr Pro Lys Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15
```

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

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

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

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

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

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
        115                 120                 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
    130                 135                 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145                 150                 155                 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190

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

Gly Glu Cys
    210
```

<210> 278
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 278

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


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


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


Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60


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


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


Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380
```

```
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400


Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210> 279
<211> 105
<212> PRT
<213> Homo sapiens

<400> 279
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


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


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


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


Arg Asp Leu Arg Gly Ser Tyr Asp Tyr
            100                 105
```

<210> 280
<211> 102
<212> PRT
<213> Homo sapiens

<400> 280
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Trp Pro Arg Thr
100

<210> 281
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 281
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60

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

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

Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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> 282
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 282
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

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

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

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

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

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

Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val
100 105 110

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
115 120 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
130 135 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145 150 155 160

```
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175


Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190


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


Gly Glu Cys
    210


<210> 283
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 283
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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


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


Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60


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


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

```
Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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> 284
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 284
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

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

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

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

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

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

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
        115                 120                 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
    130                 135                 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145                 150                 155                 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190

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

Gly Glu Cys
    210
```

<210> 285
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 285
Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
50 55 60

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

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

Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365
```

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 286
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 286
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
50 55 60

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

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

```
Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu 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 Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
    210                 215                 220

Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300
```

```
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320


Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
                325                 330                 335


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350


Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400


Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210> 287
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 287
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

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

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50   55   60

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

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

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

Thr Leu Val Thr Val Ser Ser
        115

<210> 288
<211> 104
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 288
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1   5   10   15

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

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

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

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

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

Gln Gly Thr Lys Leu Glu Ile Lys
100

<210> 289
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 289
Gln Val Gln Leu Lys Glu Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
20 25 30

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

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

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

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

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
        115

<210> 290
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 290
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
            20   25   30

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

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
    50   55   60

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

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

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 291
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 291
Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

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

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

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

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65 70 75 80

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

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

<210> 292
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 292
Glu Asn Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

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

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


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


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


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


<210> 293
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 293
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Arg
            20                  25                  30


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


Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


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

Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 294
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 294
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Glu Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Tyr
20 25 30

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

Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
100 105 110

Ser

<210> 295
<211> 118

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 295
Gln Val Gln Leu Lys Glu Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
20 25 30

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

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

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

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

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 296
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 296
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

```
Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
            20                  25                  30


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


Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
    50                  55                  60


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


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


Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210> 297
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 297
Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15


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


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

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

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
65 70 75 80

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

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

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 298
Glu Asn Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

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

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

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

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

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

<210> 299
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 299
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

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

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser
35 40 45

Leu Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
50 55 60

Pro Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
100 105 110

Cys Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr
115 120 125

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
130 135 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145 150 155 160

```
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220


Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240


<210> 300
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 300
Met Gly Trp Thr Trp Ile Phe Ile Leu Ile Leu Ser Val Thr Thr Gly
1               5                   10                  15


Val His Ser Glu Val Gln Leu Leu Gln Ser Gly Pro Glu Leu Glu Lys
            20                  25                  30


Pro Gly Ala Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe
        35                  40                  45


Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu
    50                  55                  60


Glu Trp Ile Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
65                  70                  75                  80


Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95
```

```
Thr Ala Tyr Met His Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300
```

```
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        435                 440                 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460
```

<210> 301
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 301

Gln Val Gln Leu Val Glu 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

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

Gly Trp Ile Asn Ala Gly Asn Gly Tyr Arg Lys Tyr Ser Gln Lys Phe
50 55 60

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

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

Ala Arg Phe Glu Gly Gly Met Val Thr Ala Met Asp Phe Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 302
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 302
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Arg
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

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

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

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

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

<210> 303
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 303
Glu Val Gln Leu Leu Glu 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

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

Gly Trp Ile Asn Ala Gly Asn Gly Tyr Arg Lys Tyr Ser Gln Lys Phe
50 55 60

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

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

Ala Arg Phe Glu Gly Gly Met Val Thr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 304
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 304
Asp Ile Gln Val Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

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

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

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

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

<210> 305
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 305
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

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

Gly Ile Ile Asn Pro Ser Ala Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Asp Arg Val Thr Met Thr Arg Asp Thr Ser Arg Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Arg Val Val Val Gly Gly Pro Phe Asp Phe Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 306
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 306
Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

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


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


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


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


Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys



<210> 307
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 307
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe Ile Ser Tyr
            20                  25                  30


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


Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
```

```
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Ile Tyr
65                  70                  75                  80


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


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


Thr Leu Val Thr Val Ser Ser
        115


<210> 308
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 308
Asp Val Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


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


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


Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


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


Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
                85                  90                  95


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

Lys

<210> 309
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 309
Gln Val Gln Leu Val Glu 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 Ala Arg Tyr
20 25 30

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

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Val Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

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

Thr Leu Val Thr Val Ser Ser
115

<210> 310
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 310
Asp Ile Arg Val Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

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

Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 311
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 311
Glu Val Gln Leu Leu Glu 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 Arg Tyr
            20   25   30

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

Gly Ile Ile Asn Pro Ser Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

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

Ala Arg Arg Val Val Val Gly Gly Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 312
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 312
Asp Ile Gln Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Ile Leu Tyr Ser
            20   25   30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60

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

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

Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 313
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 313
Glu Val Gln Leu Leu Glu 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 Ile Phe Ser Arg Tyr
20 25 30

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

Gly Trp Ile Asn Pro Phe Asn Gly Phe Thr Lys Tyr Ser Gln Lys Phe
50 55 60

Gln Gly Arg Val Ala Leu Thr Arg Asp Arg Ser Ala Thr Thr Gly Tyr
65 70 75 80

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

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

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 314
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 314
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Thr Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

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

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

Ser Thr Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 315
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 315
Gln Val Gln Leu Leu Glu 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

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

Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Ile Tyr Ser Gln Lys Phe
50 55 60

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

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

Ala Arg Trp Val Gly Gly Val Ala Ser Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 316
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 316
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Arg
20 25 30

```
Asn Gly Tyr Asn Tyr Phe Asp Trp Tyr Leu Gln Gln Pro Gly Gln Ser
        35                  40                  45


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


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


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


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


<210> 317
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 317
Gln Val Gln Leu Leu Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Glu Ala Ser Gly Tyr Thr Phe Thr Ser Ser
            20                  25                  30


Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

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

Ala Arg Glu Arg Pro Arg Arg Arg Gly Gly Gly Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 318
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 318
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Glu Ala Ser Gly Tyr Thr Phe Thr Ser Ser
20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Lys Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Glu Arg Pro Arg Arg Arg Gly Gly Gly Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 319
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 319
Asp Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Thr 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 Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Trp
85 90 95

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

<210> 320
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 320
Gln Val Gln Leu Val Glu 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 Asn Tyr
            20                  25                  30


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


Gly Ile Ile Asn Pro Ser Arg Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


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


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


Thr Leu Val Thr Val Ser Ser
        115


<210> 321
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 321
Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


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


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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

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

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

Lys

<210> 322
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 322
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

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

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser
35 40 45

Leu Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
50 55 60

Pro Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

```
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
            100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr
        115                 120                 125

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240


<210> 323
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 323
Met Gly Trp Thr Trp Ile Phe Ile Leu Ile Leu Ser Val Thr Thr Gly
1               5                   10                  15
```

```
Val His Ser Glu Val Gln Leu Leu Gln Ser Gly Pro Glu Leu Glu Lys
            20                  25                  30

Pro Gly Ala Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe
        35                  40                  45

Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met His Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220
```

```
Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240


Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255


Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270


Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285


Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300


Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320


Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335


Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365


Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415


Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430
```

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 324
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 324
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1 5 10 15

Ser Leu Ser Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
20 25 30

Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
35 40 45

Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
50 55 60

Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Ser
65 70 75 80

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
100 105 110

Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys
115 120 125

Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130 135 140

```
Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160


Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175


Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190


Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205


Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220


Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210> 325
<211> 595
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 325
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1               5                   10                  15


Ser Leu Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Glu Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe
        35                  40                  45


Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu
    50                  55                  60
```

```
Glu Trp Ile Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met His Leu Lys Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270
```

```
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        435                 440                 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ala Pro
    450                 455                 460

Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu
465                 470                 475                 480
```

Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro
485 490 495

Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala
500 505 510

Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu
515 520 525

Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro
530 535 540

Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly
545 550 555 560

Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile
565 570 575

Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile Ile Ser
580 585 590

Thr Leu Thr
595

<210> 326
<211> 105
<212> PRT
<213> Homo sapiens

<400> 326
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

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

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

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

Arg Asp Leu Arg Gly Ser Tyr Asp Tyr
100 105

<210> 327
<211> 102
<212> PRT
<213> Homo sapiens

<400> 327
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Trp Pro Arg Thr
100

<210> 328
<211> 569
<212> PRT
<213> Homo sapiens

<400> 328
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

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

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

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

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

Ile Val Ser Ser Gly Ser Ala Ser Ala Pro Thr Leu Phe Pro Leu Val
        115   120   125

Ser Cys Glu Asn Ser Pro Ser Asp Thr Ser Ser Val Ala Val Gly Cys
    130   135   140

Leu Ala Gln Asp Phe Leu Pro Asp Ser Ile Thr Phe Ser Trp Lys Tyr
145   150   155   160

Lys Asn Asn Ser Asp Ile Ser Ser Thr Arg Gly Phe Pro Ser Val Leu
                165   170   175

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

Asp Val Met Gln Gly Thr Asp Glu His Val Val Cys Lys Val Gln His
        195   200   205

```
Pro Asn Gly Asn Lys Glu Lys Asn Val Pro Leu Pro Val Ile Ala Glu
    210                 215                 220

Leu Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe
225                 230                 235                 240

Gly Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser
                245                 250                 255

Pro Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly
            260                 265                 270

Ser Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly
        275                 280                 285

Pro Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp
    290                 295                 300

Trp Leu Ser Gln Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu
305                 310                 315                 320

Thr Phe Gln Gln Asn Ala Ser Ser Met Cys Val Pro Asp Gln Asp Thr
                325                 330                 335

Ala Ile Arg Val Phe Ala Ile Pro Pro Ser Phe Ala Ser Ile Phe Leu
            340                 345                 350

Thr Lys Ser Thr Lys Leu Thr Cys Leu Val Thr Asp Leu Thr Thr Tyr
        355                 360                 365

Asp Ser Val Thr Ile Ser Trp Thr Arg Gln Asn Gly Glu Ala Val Lys
    370                 375                 380

Thr His Thr Asn Ile Ser Glu Ser His Pro Asn Ala Thr Phe Ser Ala
385                 390                 395                 400

Val Gly Glu Ala Ser Ile Cys Glu Asp Asp Trp Asn Ser Gly Glu Arg
                405                 410                 415
```

```
Phe Thr Cys Thr Val Thr His Thr Asp Leu Pro Ser Pro Leu Lys Gln
            420                 425                 430

Thr Ile Ser Arg Pro Lys Gly Val Ala Leu His Arg Pro Asp Val Tyr
        435                 440                 445

Leu Leu Pro Pro Ala Arg Glu Gln Leu Asn Leu Arg Glu Ser Ala Thr
    450                 455                 460

Ile Thr Cys Leu Val Thr Gly Phe Ser Pro Ala Asp Val Phe Val Gln
465                 470                 475                 480

Trp Met Gln Arg Gly Gln Pro Leu Ser Pro Glu Lys Tyr Val Thr Ser
                485                 490                 495

Ala Pro Met Pro Glu Pro Gln Ala Pro Gly Arg Tyr Phe Ala His Ser
            500                 505                 510

Ile Leu Thr Val Ser Glu Glu Glu Trp Asn Thr Gly Glu Thr Tyr Thr
        515                 520                 525

Cys Val Val Ala His Glu Ala Leu Pro Asn Arg Val Thr Glu Arg Thr
    530                 535                 540

Val Asp Lys Ser Thr Gly Lys Pro Thr Leu Tyr Asn Val Ser Leu Val
545                 550                 555                 560

Met Ser Asp Thr Ala Gly Thr Cys Tyr
                565
```

<210> 329
<211> 219
<212> PRT
<213> Homo sapiens

<400> 329

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

```
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
            20                  25                  30

Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
    50                  55                  60

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

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

Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 330
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 330

```
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15

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

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser
        35                  40                  45

Leu Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
            100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr
        115                 120                 125

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175
```

```
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220


Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240


<210> 331
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 331
Met Gly Trp Thr Trp Ile Phe Ile Leu Ile Leu Ser Val Thr Thr Gly
1               5                   10                  15


Val His Ser Glu Val Gln Leu Leu Gln Ser Gly Pro Glu Leu Glu Lys
            20                  25                  30


Pro Gly Ala Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe
        35                  40                  45


Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu
    50                  55                  60


Glu Trp Ile Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
65                  70                  75                  80


Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95
```

```
Thr Ala Tyr Met His Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300
```

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305 310 315 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
325 330 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
340 345 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
355 360 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
370 375 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385 390 395 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
405 410 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 332
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 332
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Glu Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Tyr
            20   25   30

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

Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50   55   60

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

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

Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            100   105   110

Ser

<210> 333
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 333
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Arg
            20   25   30

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

Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

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

Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 334
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 334
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

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

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Ser
35 40 45

Leu Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
50 55 60

Pro Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

```
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
            100                 105                 110

Cys Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr
        115                 120                 125

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240


<210> 335
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 335
Met Gly Trp Thr Trp Ile Phe Ile Leu Ile Leu Ser Val Thr Thr Gly
1               5                   10                  15
```

```
Val His Ser Glu Val Gln Leu Leu Gln Ser Gly Pro Glu Leu Glu Lys
            20                  25                  30

Pro Gly Ala Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe
        35                  40                  45

Thr Gly Tyr Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met His Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220
```

```
Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240


Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255


Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270


Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285


Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300


Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320


Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335


Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365


Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415


Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430
```

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 336
<211> 137
<212> PRT
<213> Mus musculus

<400> 336
Met Lys Leu Trp Leu Asn Trp Ile Phe Leu Val Thr Leu Leu Asn Gly
1 5 10 15

Phe Gln Cys Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Leu
20 25 30

Pro Gly Asp Ser Leu Arg Leu Ser Cys Ala Thr Ser Glu Phe Thr Phe
35 40 45

Thr Asp Tyr Tyr Met Thr Trp Val Arg Gln Pro Pro Arg Lys Ala Leu
50 55 60

Glu Trp Leu Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu
65 70 75 80

Tyr Asn Pro Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Gln Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Thr Glu Asp Ser Ala
100 105 110

Thr Tyr Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly
115 120 125

Gln Thr Thr Leu Thr Val Ser Ser Ala
130 135

<210> 337
<211> 133

<212> PRT
<213> Mus musculus

<400> 337
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Gly
1   5   10   15

Ser Ser Ser Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
            20   25   30

Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
        35   40   45

Leu Lys Asn Asn Gly Asn Thr Phe Leu His Trp Tyr Leu Gln Lys Ser
    50   55   60

Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser
65   70   75   80

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Tyr Phe Thr
                85   90   95

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
            100   105   110

Ser Gln Ser Thr His Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
        115   120   125

Glu Leu Lys Arg Thr
    130

<210> 338
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 338
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1   5   10   15

```
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Lys Asn
            20                  25                  30

Asn Gly Asn Thr Phe Leu His Trp Tyr Leu Gln Lys Ser Gly Gln Ser
        35                  40                  45

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

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

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

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

<210> 339
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 339

```
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Leu Pro Gly Asp
1               5                   10                  15

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

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

Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu Tyr Asn Pro
    50                  55                  60
```

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

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

Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 340
<211> 112
<212> PRT
<213> Mus musculus

<400> 340
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Lys Asn
20 25 30

Asn Gly Asn Thr Phe Leu His Trp Tyr Leu Gln Lys Ser Gly Gln Ser
35 40 45

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

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

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

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

<210> 341
<211> 119

<212> PRT
<213> Mus musculus

<400> 341
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Leu Pro Gly Asp
1   5   10   15

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

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

Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu Tyr Asn Pro
    50   55   60

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

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

Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Thr Leu Thr Val Ser Ser
        115

<210> 342
<211> 112
<212> PRT
<213> Mus musculus

<400> 342
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Asp Gln
1   5   10   15

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Leu Gly Lys Asn
            20   25   30

Asn Gly Asn Thr Phe Leu His Trp Tyr Leu Gln Lys Ser Gly Gln Ser
        35   40   45

```
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val Pro
    50                  55                  60

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

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

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

<210> 343
<211> 119
<212> PRT
<213> Mus musculus

<400> 343

```
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Leu Pro Gly Asp
1               5                   10                  15

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

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

Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu Tyr Asn Pro
    50                  55                  60

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

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

Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
```

Thr Thr Leu Thr Val Ser Ser
        115

<210> 344
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 344
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1   5   10   15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Lys Asn
            20   25   30

Asn Gly Asn Thr Phe Leu His Trp Tyr Leu Gln Lys Ser Gly Gln Ser
        35   40   45

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

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

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

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

<210> 345
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 345

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

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

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

Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu Tyr Asn Pro
50 55 60

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

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

Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 346
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 346
Glu 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 Thr Phe Thr Asp Tyr
20 25 30

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

Gly Asp Ile Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50   55   60

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

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

Ala Thr Tyr Gly Leu Gly Gly Tyr Trp Gly Gln Gly Thr Thr Leu Thr
            100   105   110

Val Ser Ser
        115

<210> 347
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 347
Gly Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val
1   5   10   15

Gly Glu Arg Val Thr Gln Thr Cys Lys Ala Ser Glu Asn Val Val Thr
            20   25   30

Tyr Val Ser Trp Tyr Gln Leu Lys Pro Glu Gln Ser Pro Lys Leu Leu
        35   40   45

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

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

Ala Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Gly Tyr Ser Tyr Pro
85 90 95

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

<210> 348
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 348
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

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

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

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

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

Val Ser Ser
115

<210> 349
<211> 111

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 349
Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu
1 5 10 15

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

Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro
35 40 45

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

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

His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile
85 90 95

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

<210> 350
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 350
Glu 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 Thr Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr Gly Tyr Asn Gln Lys Phe
50 55 60

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

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

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

Thr Val Ser
115

<210> 351
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 351
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

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

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

Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 352
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 352
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Thr
1 5 10 15

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

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

Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

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

Leu Gln Leu Asn Asn Leu Thr Ser Glu Asn Ser Ala Val Tyr Phe Cys
85 90 95

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

Val Thr Val Ser Ser
115

<210> 353
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 353
Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

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

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

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

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

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Glu Val Lys Leu
100 105 110

Gln Glu Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met
115 120 125

Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Asp Tyr Val Val His Trp
130 135 140

Leu Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn
145 150 155 160

Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala
165 170 175

Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Val Ser
180 185 190

Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Asp Tyr
195 200 205

Arg Tyr Glu Val Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
210 215 220

Thr Val Ser Ser
225

<210> 354
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 354
Glu Val Lys Leu Gln Glu Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Asp Tyr
20 25 30

Val Val His Trp Leu 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 Val Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Tyr Glu Val Tyr Gly Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 355
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 355
Asp Ile Val Leu Thr Gln Ser Pro Thr Ile Met Ser Ala Ser Pro Gly
1 5 10 15

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

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

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

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

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

Phe Gly Asp Gly Thr Arg Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
100 105 110

Thr Val Ser
115

<210> 356
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 356
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Val Val 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

Tyr Ile His Trp Ile Lys Gln Thr Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

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

Lys Gly 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 Tyr Cys
85 90 95

Ala Arg Glu Val Arg Leu Arg Tyr Phe Asp Val Trp Gly Ala Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 357
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 357

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Phe Phe Ser
20 25 30

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ser Glu Asp Leu Ala Ile Tyr Tyr Cys His Gln
85 90 95

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

Arg

<210> 358
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 358
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 Ser Phe Pro Asp Tyr
20 25 30

Tyr Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Tyr Phe Ala Ser Gly Asn Ser Glu Tyr Asn Gln Lys Phe
50 55 60

Thr Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

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

Ala Ser Leu Tyr Asp Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 359
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 359
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Val His Ser
20 25 30

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

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

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

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

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

<210> 360
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 360
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 Ser Phe Pro Asp Tyr
20 25 30

Tyr Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Tyr Phe Ala Ser Gly Asn Ser Glu Tyr Asn Gln Lys Phe
50 55 60

Thr Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Ser Leu Tyr Asp Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 361
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 361
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Val His Ser
20 25 30

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

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

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

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

Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 362
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 362
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe
50 55 60

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

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

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

Val Thr Val Ser Ser
115

<210> 363
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 363
Asp Ile Val Leu Thr Gly Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1 5 10 15

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

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

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

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


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


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


<210> 364
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 364
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15


Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
            20                  25                  30


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


Gly Arg Ile Asn Thr Glu Thr Gly Glu Pro Leu Tyr Ala Asp Asp Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Leu Val Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
                85                  90                  95


Ser Asn Asp Tyr Leu Tyr Ser Cys Asp Tyr Trp Gly Arg Gly Thr Thr
            100                 105                 110


Leu Thr Val Ser Ser
        115
```

<210> 365
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 365
Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1 5 10 15

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

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

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

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

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

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

<210> 366
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 366
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20   25   30

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 367
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 367
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

Ser Arg 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 His Tyr Thr Thr Pro Pro
                85                  90                  95

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

<210> 368
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 368

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

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

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

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

Ser Arg 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 His Tyr Thr Thr Pro Pro
                85                  90                  95

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

<210> 369
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 369
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 370
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 370
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

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

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

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

<210> 371
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 371
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

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

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

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

Ala Arg Asp Arg Gly Gly Ala Val Ser Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 372
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 372
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

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

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

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

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

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

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

<210> 373
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 373
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

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

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

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

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

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

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

Gly Ala Ser Val Thr Val Ser Ser
115 120

<210> 374
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 374
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu
20

<210> 375
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 375
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Val
1 5 10 15

Asp Arg Ile Ser
20

<210> 376
<211> 107
<212> PRT
<213> Mus musculus

<400> 376
Asp Thr Val Met Thr Gln Ser His Lys Ile Met Ser Thr Ser Val Gly
1 5 10 15

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

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

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

```
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80


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


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


<210> 377
<211> 119
<212> PRT
<213> Mus musculus

<400> 377
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Thr
1               5                   10                  15


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
            20                  25                  30


Thr Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45


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


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


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


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


Thr Thr Leu Thr Val Ser Ser
        115
```

<210> 378
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 378
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 379
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 379
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser
        115

<210> 380
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 380
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

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

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

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

<210> 381
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 381
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser
        115

<210> 382
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 382
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val 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> 383
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 383
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

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

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

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

```
Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe 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 Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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 Glu Glu Met 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

<210> 384
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 384
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Ser Arg 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 His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val 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> 385
<211> 449

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 385

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


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


Gly Thr Leu 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 Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380
```

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 386
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 386
Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
1 5 10 15

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

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

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

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

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

```
Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
        115                 120                 125


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


Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160


Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
                165                 170                 175


Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
            180                 185                 190


Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
        195                 200                 205


Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 387
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 387
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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

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

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

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

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

Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe 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 Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly 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 Ala Leu Pro Ala Pro 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 Glu Glu Met 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> 388
<211> 124
<212> PRT
<213> Homo sapiens

<400> 388
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

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

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

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

Ala Lys Gly Phe Gln Tyr Gly Ser Gly Ser Tyr Tyr Thr His Phe Asp
            100 105 110

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

<210> 389
<211> 107
<212> PRT
<213> Homo sapiens

<400> 389
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Ser 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 Ser Ser Leu Gln Pro
65                  70                  75                  80

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

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


<210> 390
<211> 122
<212> PRT
<213> Homo sapiens

<400> 390
Gln Val Gln Leu Val Glu 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 Ser Ser Tyr
            20                  25                  30

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

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

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

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

```
Ala Arg Asn Tyr Gly Leu Gly Ser Tyr Tyr Asn Tyr Phe Asp Phe Trp
            100                 105                 110


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


<210> 391
<211> 107
<212> PRT
<213> Homo sapiens

<400> 391
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


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


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


Tyr Ala Ala Ser Ser 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 Ser Ser Leu Gln Pro
65                  70                  75                  80


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


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


<210> 392
<211> 122
<212> PRT
<213> Homo sapiens

<400> 392
Gln Val Gln Leu Val Glu 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 Ser Ser Tyr
            20                  25                  30


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


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


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


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


Ala Leu Met Val Arg Gly Leu Ile Ile Thr Gly Tyr Phe Asp Tyr Trp
            100                 105                 110


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


<210> 393
<211> 108
<212> PRT
<213> Homo sapiens

<400> 393
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser 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 Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

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

<210> 394
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 394
Asp Thr Val Met Thr Gln Ser His Lys Ile Met Ser Thr Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 395
<211> 109

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 395
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

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

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

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

<210> 396
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 396
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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


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


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


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


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


<210> 397
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 397
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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

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


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


Gly Thr Leu 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> 398
<211> 109
<212> PRT
<213> Homo sapiens

<400> 398
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


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

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


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


Ser Arg 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 His Tyr Thr Thr Pro Pro
                85                  90                  95


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


<210> 399
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 399
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1               5                   10                  15


Val Ile Ile Ser Arg Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30


Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45


Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
65                  70                  75                  80
```

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
85 90 95

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

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135 140

<210> 400
<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 400
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Ile Ser Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg
130

<210> 401
<211> 472
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 401
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Ile Ser Arg Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
65 70 75 80

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
85 90 95

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

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
115 120 125

```
Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

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

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335
```

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

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 402
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 402
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Ile Ser Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

```
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 403
<211> 628
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 403
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Ile Ser Arg Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
65 70 75 80

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
85 90 95

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

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
115 120 125

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
130 135 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145 150 155 160

```
Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

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

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

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

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365
```

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys Thr Gln Asp Cys Ser Phe Gln His
465                 470                 475                 480

Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp
                485                 490                 495

Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp
            500                 505                 510

Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp
        515                 520                 525

Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu
    530                 535                 540

Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln
545                 550                 555                 560

Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu
                565                 570                 575
```

Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr
580 585 590

Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser
595 600 605

Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala Thr Ala
610 615 620

Pro Thr Ala Pro
625

<210> 404
<211> 643
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 404
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Ile Ser Arg Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
65 70 75 80

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
85 90 95

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

```
Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
        115                 120                 125

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

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

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320
```

```
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

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

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly
465                 470                 475                 480

Gly Ser Gly Gly Gly Gly Ser Thr Gln Asp Cys Ser Phe Gln His Ser
                485                 490                 495

Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu Ser Asp Tyr
            500                 505                 510

Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu Gln Asp Glu
        515                 520                 525
```

```
Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln Arg Trp Met
    530                 535                 540

Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly Leu Leu Glu
545                 550                 555                 560

Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala Phe Gln Pro
                565                 570                 575

Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser Arg Leu Leu
            580                 585                 590

Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp Ile Thr Arg
        595                 600                 605

Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro Asp Ser Ser
    610                 615                 620

Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala Thr Ala Pro
625                 630                 635                 640

Thr Ala Pro
```

<210> 405
<211> 214
<212> PRT
<213> Mus musculus

<400> 405

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

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val 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> 406
<211> 220
<212> PRT
<213> Mus musculus

<400> 406
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

Gly Thr Leu 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 Thr 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
    210                 215                 220
```

<210> 407
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 407
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
20 25 30

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val
35 40 45

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

Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
85 90 95

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile
100 105 110

Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
115 120 125

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145 150 155 160

```
Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
                165                 170                 175


Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
            180                 185                 190


Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
        195                 200                 205


Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
    210                 215                 220


Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210> 408
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 408
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15


Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30


Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


Thr Asp Tyr Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn
65                  70                  75                  80


Gln Arg Phe Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn
                85                  90                  95
```

```
Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp
        115                 120                 125

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
                245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300
```

```
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly
465
```

<210> 409
<211> 219
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 409
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Ser Arg 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 His Tyr Thr Thr Pro Pro
85 90 95

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

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 410
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 410
Gln Val Gln Leu Leu Glu Glu Val Gln Leu Val Glu Ser Gly Gly Gly
1 5 10 15

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

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

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
50 55 60

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

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

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
100 105 110

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ala
115 120 125

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

```
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160


Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175


Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190


Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205


Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220


Ser Cys Asp Lys His His His His His His
225                 230


<210> 411
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 411
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30


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


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

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


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


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


Gly Thr Leu 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 Glu Leu Leu Gly Gly
225                 230                 235                 240


Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270
```

```
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> 412
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 412
```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


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


Gly Thr Leu Val Thr Val Ser Ser Cys 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 Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400
```

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 413
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 413
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

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

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

Ser Arg 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 His Tyr Thr Thr Pro Pro
85 90 95

```
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Cys 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> 414
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 414
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15


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


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

Gly Leu Ile Tyr Pro Gly Asp Ser Asp Thr Lys Tyr Ser Pro Ser Phe
    50   55   60

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

Leu Gln Trp Ser Ser Leu Lys Pro Ser Asp Ser Ala Val Tyr Phe Cys
                85   90   95

Ala Arg His Asp Val Gly Tyr Cys Thr Asp Arg Thr Cys Ala Lys Trp
            100   105   110

Pro Glu Trp Leu Gly Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
        115   120   125

Ser

<210> 415
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 415
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 His Thr Asn Arg Pro Ala Gly Val Pro Asp Arg Phe Ser
    50   55   60

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Tyr Thr Leu
85 90 95

Ser Gly Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 416
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 416
Glu Val Gln Leu Leu Glu Trp Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

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

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

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

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

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

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

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 417
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 417
Glu Leu Thr Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

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

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

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

Gly Gly Ser Glu 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 Arg Val Pro Leu
85 90 95

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

<210> 418
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 418
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

Gly Thr Leu 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 Pro Lys Ser Cys
    210                 215                 220
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430
```

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435   440   445

Pro Gly Lys
    450

<210> 419
<211> 469
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 419
Met Glu Cys Ser Trp Val Met Leu Phe Leu Leu Ser Val Thr Ala Gly
1   5   10   15

Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20   25   30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile
        35   40   45

Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50   55   60

Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala
65   70   75   80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn
                85   90   95

Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100   105   110

Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr
        115   120   125

```
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
    210                 215                 220

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225                 230                 235                 240

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
                245                 250                 255

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
305                 310                 315                 320

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                325                 330                 335
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
            340                 345                 350


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365


Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
    370                 375                 380


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460


Leu Ser Pro Gly Lys
465


<210> 420
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Antibody variable domain

<400> 420
Met Glu Trp Ser Cys Val Met Leu Phe Leu Leu Ser Val Thr Ala Gly
1               5                   10                  15


Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
            20                  25                  30
```

```
Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val
        35                  40                  45

Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
    50                  55                  60

Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg
65                  70                  75                  80

Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
                85                  90                  95

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr
            100                 105                 110

Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
        115                 120                 125

Val Ala Ala Pro Ser Val Phe Ile Phe Glu Pro Ser Asp Glu Gln Leu
    130                 135                 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145                 150                 155                 160

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

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
            180                 185                 190

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
        195                 200                 205

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
    210                 215                 220

Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230
```

<210> 421
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Antibody variable domain

<400> 421
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

Gly Thr Leu 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 Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365
```

```
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> 422
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 422

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

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

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

Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn Tyr Asn Ser Ala Leu Lys
    50                  55                  60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80
```

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

Arg Glu His Tyr Tyr Gly Ser Ser Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

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

Ser Gly Gly Gly Gly Ser Gly Ile Val Met Thr Gln Ser Pro Leu Ser
    130                 135                 140

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

Gln Ser Ile Val His Ser Tyr Gly Asn Thr Tyr Leu Phe Trp Tyr Leu
                165                 170                 175

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Arg Val Ser Asn
            180                 185                 190

Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asn Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Met Gly Val
    210                 215                 220

Tyr Tyr Cys Phe Gln Gly Thr His Val Pro Tyr Thr Phe Gly Gly Gly
225                 230                 235                 240

Thr Lys Leu Glu Ile Lys
                245
```

<210> 423
<211> 246
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 423
Gln Val Gln Leu Gln Gln Ser Gly Ala 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 Tyr
20 25 30

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

Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Thr Tyr Asn Gly Lys Phe
50 55 60

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

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

Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

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

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

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

Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser Phe Met His Trp Tyr Gln
165 170 175

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

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

Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Thr Asp Asp Val Ala Thr
210 215 220

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

Thr Lys Leu Glu Ile Lys
245

<210> 424
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 424
Asp Val Gln Leu Gln Glu Ser Gly Pro Val Leu Val Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Thr Ala Ser Gly Tyr Thr Phe Thr Asp His
20 25 30

Phe Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg His Asn Trp Gly Ala Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

```
Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val
    130                 135                 140


Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys
145                 150                 155                 160


Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln
                165                 170                 175


Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile Tyr Tyr Met Ser Asn Leu
            180                 185                 190


Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp
        195                 200                 205


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


Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Leu Glu Ile Lys
                245


<210> 425
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 425
Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1               5                   10                  15
```

```
Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

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

Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser Phe Asp Tyr Trp Gly Gln
            100                 105                 110

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

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

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

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

Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly
            180                 185                 190

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

Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln
    210                 215                 220
```

Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
225 230 235 240

Ile Asn

<210> 426
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 426
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 Phe Ser Leu Thr Ser Tyr
20 25 30

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

Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met Asp Tyr Trp Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

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

```
Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
145                 150                 155                 160


Ala Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr Tyr Ala Trp Tyr
                165                 170                 175


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


Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205


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


Tyr Tyr Cys Phe Gln Gly Thr His Val Pro Tyr Thr Phe Phe Gly Gln
225                 230                 235                 240


Gly Thr Lys Leu Glu Ile Lys Arg
                245


<210> 427
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 427
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


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

```
Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

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

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

Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr Phe Asp Tyr Trp Trp Gly
            100                 105                 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

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

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
145                 150                 155                 160

Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser Phe Ala Trp Tyr Gln
                165                 170                 175

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

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

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

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

Thr Lys Leu Glu Ile Lys Arg
                245
```

<210> 428
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 428

```
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 Thr Phe Thr Asp His
            20                  25                  30

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

Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

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

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

Ala Arg His Asn Trp Gly Ala Tyr Phe Asp Tyr Trp Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

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

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Ala Trp Tyr Gln Gln
                165                 170                 175
```

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


Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        195                 200                 205


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


Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr Phe Phe Gly Gln Gly Thr
225                 230                 235                 240


Lys Leu Glu Ile Lys Arg
                245


<210> 429
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 429
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 Thr Phe Thr Asp Tyr
            20                  25                  30


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


Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

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

Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser Phe Asp Tyr Trp Trp Gly
            100                 105                 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

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

Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
145                 150                 155                 160

Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

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

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

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

Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240

Ile Lys Arg
```

<210> 430
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 430
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50   55   60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp
            100   105   110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly
        115   120   125

Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
    130   135   140

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Trp Ser
145   150   155   160

Tyr Leu Asn Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Asn Leu Leu
                165   170   175

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

Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
        195   200   205

```
Ala Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro
    210                 215                 220


Gln Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
225                 230                 235


<210> 431
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 431
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile Tyr
            20                  25                  30


Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45


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


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


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


Arg His Ser Gly Tyr Gly Thr His Trp Gly Val Leu Phe Ala Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly
        115                 120                 125
```

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


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


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


Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Ile Leu His
            180                 185                 190


Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
        195                 200                 205


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


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


Leu Glu Ile Lys Ala
                245


<210> 432
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 432
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile Tyr
            20                  25                  30


Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45
```

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

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

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

Arg His Ser Gly Tyr Gly Ser Ser Tyr Gly Val Leu Phe Ala Tyr Trp
            100                 105                 110

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

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

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

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

Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Ile Leu His
            180                 185                 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
        195                 200                 205

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

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

Leu Glu Ile Lys Ala
                245
```

<210> 433
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 433
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Tyr Ile Ser Ser Asp Ser Ser Ala Ile Tyr Tyr Ala Asp Thr 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 Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Gly Arg Gly Arg Glu Asn Ile Tyr Tyr Gly Ser Arg Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

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

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

Lys Ala Ser Gln Asn Val Asp Thr Asn Val Ala Trp Tyr Gln Gln Lys
165 170 175

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

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205

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

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

Leu Glu Ile Lys

<210> 434
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 434
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 Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

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

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

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

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

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

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

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

Arg Ser Asn Trp Pro Pro Ser Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Arg
```

<210> 435
<211> 248
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 435

```
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 Gly Thr Phe Ser Ser Tyr
            20                  25                  30


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


Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
            100                 105                 110


Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140


Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160


Gly Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175


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

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
195 200 205

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

Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro Thr Trp Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Leu Glu Ile Lys Arg
245

<210> 436
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 436
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

```
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


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


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160


Val Gly Gly Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175


Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205


Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn
    210                 215                 220


Asn Trp Pro Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240


Lys Arg



<210> 437
<211> 518
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 437
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15
```

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

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

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

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

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

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
        115                 120                 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
    130                 135                 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145                 150                 155                 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190

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

Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
    210                 215                 220
```

```
Leu Val Gln Ser Gly Gly Gly Leu Thr Leu Ser Lys Ala Asp Tyr Glu
225                 230                 235                 240


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                245                 250                 255


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser
            260                 265                 270


Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val
        275                 280                 285


Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr
    290                 295                 300


Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Lys
305                 310                 315                 320


Cys Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn
                325                 330                 335


Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser
            340                 345                 350


Lys Asn Thr Ala Phe Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr
        355                 360                 365


Gly Val Tyr Phe Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp
    370                 375                 380


Tyr Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly
385                 390                 395                 400


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
                405                 410                 415


Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            420                 425                 430
```

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
435 440 445

Thr Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
450 455 460

Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
465 470 475 480

Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr
485 490 495

Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Cys Gly Thr
500 505 510

Lys Leu Gln Ile Thr Arg
515

<210> 438
<211> 524
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 438
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

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

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

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

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

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

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
        115                 120                 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
    130                 135                 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145                 150                 155                 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
                165                 170                 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            180                 185                 190

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

Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser His
    210                 215                 220

Val Lys Leu Gln Glu Ser Gly Pro Leu Thr Leu Ser Lys Ala Asp Tyr
225                 230                 235                 240

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
                245                 250                 255

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly
            260                 265                 270

Ser Gly Gly Gly Gly Ser Ala Ser His Val Lys Leu Gln Glu Ser Gly
        275                 280                 285
```

```
Pro Gly Leu Val Gln Pro Ser Gln Ser Leu Ser Leu Thr Cys Thr Val
    290                 295                 300

Ser Gly Phe Ser Leu Thr Asp Tyr Gly Val His Trp Val Arg Gln Ser
305                 310                 315                 320

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Gly
                325                 330                 335

Thr Ala Tyr Asn Thr Ala Leu Ile Ser Arg Leu Asn Ile Tyr Arg Asp
            340                 345                 350

Asn Ser Lys Asn Gln Val Phe Leu Glu Met Asn Ser Leu Gln Ala Glu
        355                 360                 365

Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Gly Ser Tyr Pro Tyr Asn
    370                 375                 380

Tyr Phe Asp Ala Trp Gly Cys Gly Thr Thr Val Thr Val Ser Ser Gly
385                 390                 395                 400

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ala
                405                 410                 415

Val Val Ile Gln Glu Ser Ala Leu Thr Thr Pro Pro Gly Glu Thr Val
            420                 425                 430

Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ala Ser Asn Tyr
        435                 440                 445

Ala Asn Trp Val Gln Glu Lys Pro Asp His Cys Phe Thr Gly Leu Ile
    450                 455                 460

Gly Gly His Asn Asn Arg Pro Pro Gly Val Pro Ala Arg Phe Ser Gly
465                 470                 475                 480

Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Ala Gly Thr Gln Thr
                485                 490                 495
```

Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asp His Trp
500 505 510

Val Ile Gly Gly Gly Thr Arg Leu Thr Val Leu Gly
515 520

<210> 439
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 439
His Met Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro
1 5 10 15

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

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

Trp Ile Gly Glu Ile Asn Pro Met Asp Ser Arg Thr Asn Tyr Asn Lys
50 55 60

Lys Phe Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr
65 70 75 80

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

Tyr Cys Ala Arg Pro Gly Arg Ala Arg Gly Met Asp Tyr Trp Gly Gln
100 105 110

Gly Asn Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Asn Ile Val Leu Thr Gln Ser Pro
130 135 140

Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Ile Ile Ser Cys Leu
145 150 155 160

Tyr Gly Glu Ser Val Glu Ser Tyr Gly Asn Asn Phe Met His Trp Tyr
165 170 175

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

Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg
195 200 205

Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu Ala Asp Asp Ala Ala
210 215 220

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

Thr Lys Leu Glu Ile Lys Lys Ala
245

<210> 440
<211> 225
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 440
Glu 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 Thr Phe Thr Asp Tyr
20 25 30

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

```
Gly Asp Ile Asn Pro Asn Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

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

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

Ala Thr Tyr Gly Leu Gly Gly Tyr Trp Gly Gln Gly Thr Thr Leu Thr
            100                 105                 110

Val Ser Ser Gly Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser
        115                 120                 125

Met Ser Val Gly Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Glu Asn
    130                 135                 140

Val Val Thr Tyr Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro
145                 150                 155                 160

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

Arg Phe Thr Gly Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser
            180                 185                 190

Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Gly Tyr
        195                 200                 205

Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Val Lys Lys
    210                 215                 220

Ala
225
```

<210> 441
<211> 244

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 441

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

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

Tyr Ala Met Ser Trp Ala Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp
        35                  40                  45

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

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

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

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

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

Gly Gly Ser Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
    130                 135                 140

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

Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro
                165                 170                 175
```

Gly Gln Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
195 200 205

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys
210 215 220

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

Ile Lys Lys Ala

<210> 442
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 442
Met Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly
1 5 10 15

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

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

Ile Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys
50 55 60

Phe Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

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

```
Cys Ala Arg Pro Gly Arg Ala Arg Gly Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Asn Ser Val Thr Val Ser Ser Gly Asn Ile Val Leu Thr Gln Ser Pro
        115                 120                 125


Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg
    130                 135                 140


Ala Ser Glu Ser Val Glu Ser Tyr Gly Asn Asn Phe Met His Trp Tyr
145                 150                 155                 160


Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile Tyr Leu Ala Ser
                165                 170                 175


Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg
            180                 185                 190


Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu Ala Asp Asp Ala Ala
        195                 200                 205


Thr Tyr Tyr Cys Gln Gln Asn Asn Glu Asp Pro Thr Phe Gly Gly Gly
    210                 215                 220


Thr Lys Leu Glu Ile Lys
225                 230


<210> 443
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 443
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ser Val Thr Asn Tyr
            20                  25                  30

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

Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser Ala Phe Met
    50                  55                  60

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

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

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

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

Gly Ser Ser Glu Gly Ser Thr Lys Gly Glu Ile Val Met Thr Gln Thr
    130                 135                 140

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

Lys Ala Ser Gln Ser Val Ser Asn Asp Val Thr Trp Tyr Gln Gln Lys
                165                 170                 175

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

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Tyr Gly Thr Glu Phe
        195                 200                 205

Thr Phe Thr Ile Ser Ser Val Gln Ser Glu Asp Phe Ala Val Tyr Phe
    210                 215                 220
```

Cys Gln Gln Asp Tyr Ser Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
225 230 235 240

Lys

<210> 444
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 444
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Leu Pro Gly Asp
1 5 10 15

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

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

Gly Phe Ile Arg Asn Arg Ala Asn Gly Tyr Thr Thr Glu Tyr Asn Pro
50 55 60

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

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

Tyr Cys Ala Arg Val Ser Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly
100 105 110

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

Gly Ser Ser Glu Gly Ser Thr Lys Gly Asp Val Val Met Thr Gln Thr
130 135 140

```
Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys
145                 150                 155                 160


Arg Ser Ser Gln Ser Leu Leu Lys Asn Asn Gly Asn Thr Phe Leu His
                165                 170                 175


Trp Tyr Leu Gln Lys Ser Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys
            180                 185                 190


Val Ser Asn Arg Leu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
        195                 200                 205


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


Leu Gly Val Tyr Phe Cys Ser Gln Ser Thr His Ile Pro Tyr Thr Phe
225                 230                 235                 240


Gly Gly Gly Thr Lys Leu Glu Ile Lys
                245


<210> 445
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 445
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Glu Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Tyr
            20                  25                  30


Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

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

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

Val Ser Gly Met Glu Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            100                 105                 110

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

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

Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
145                 150                 155                 160

Val His Arg Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
                165                 170                 175

Gly Gln Ser Pro Lys Leu Leu Ile His Lys Val Ser Asn Arg Phe Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

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

Ser Gln Ser Thr His Val Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys
225                 230                 235                 240

Leu Glu Leu Lys
```

<210> 446
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 446
Gln Val Gln Leu Lys Glu Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
20 25 30

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

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

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

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

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

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

Ser Gly Gly Gly Gly Ser Glu Asn Val Leu Thr Gln Ser Pro Ala Ile
130 135 140

Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
145 150 155 160

Ser Ser Val Ser Ser Ser Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly
165 170 175

```
Ala Ser Pro Lys Val Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly
            180                 185                 190


Val Pro Gly Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
        195                 200                 205


Thr Ile Ser Ser Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
    210                 215                 220


Gln Tyr Ser Gly Tyr Pro Ile Thr Phe Gly Ala Gly Thr Lys Val Glu
225                 230                 235                 240


Val Lys Arg



<210> 447
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 447
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
            20                  25                  30


Asn Ile His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45


Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
    50                  55                  60


Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Phe Leu
65                  70                  75                  80
```

Lys Met Ser Ser Leu Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Asn Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Arg Ala Ser Ser Ser
145 150 155 160

Val Ser Ser Ser Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly Lys Ala
165 170 175

Pro Lys Val Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro
180 185 190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
195 200 205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr
210 215 220

Ser Gly Tyr Pro Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235 240

Arg

<210> 448
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 448
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1   5   10   15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn His
            20   25   30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85   90   95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100   105   110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115   120   125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
    130   135   140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145   150   155   160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165   170   175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
            180   185   190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195   200   205

```
Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220


Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 449
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 449
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15


Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn His
            20                  25                  30


Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95


Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110


Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125
```

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
130 135 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145 150 155 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
165 170 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
180 185 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
195 200 205

Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
210 215 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> 450
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 450
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

```
Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205

Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 451
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
```

<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 451

```
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                  10                  15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190
```

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
195 200 205

Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
210 215 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> 452
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 452
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn His
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
115 120 125

```
Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205

Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 453
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 453
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn His
            20                  25                  30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
```

```
Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205

Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235
```

<210> 454
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 454
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
115 120 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val
130 135 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145 150 155 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
165 170 175

Thr Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp
180 185 190

```
Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205


Asp Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220


Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 455
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 455
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15


Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30


Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95


Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110
```

```
Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125


Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
    130                 135                 140


Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160


Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165                 170                 175


Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190


Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205


Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220


Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 456
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 456
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15


Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn His
            20                  25                  30


Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
```

```
Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235
```

<210> 457
<211> 239

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 457
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
115 120 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
130 135 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145 150 155 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
165 170 175

Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
180 185 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
195 200 205

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
210 215 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> 458
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 458
Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn His
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
100 105 110

```
Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125


Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
    130                 135                 140


Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160


Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
                165                 170                 175


Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190


Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205


Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220


Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210> 459
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 459
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                   10                  15


Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30
```

```
Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
    130                 135                 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
                165                 170                 175

Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
            180                 185                 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
        195                 200                 205

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
    210                 215                 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235
```

<210> 460
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 460

```
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1               5                  10                  15


Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30


Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85                  90                  95


Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
            100                 105                 110


Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
        115                 120                 125


Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
    130                 135                 140


Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145                 150                 155                 160


Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile
                165                 170                 175
```

Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
180 185 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
195 200 205

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
210 215 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> 461
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 461
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn His
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95

Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
115 120 125

Pro Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val
130 135 140

Ser Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro
145 150 155 160

Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile
165 170 175

Thr Asn Tyr Asn Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp
180 185 190

Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
195 200 205

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr
210 215 220

Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> 462
<211> 100
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 462
Lys Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn His
20 25 30

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
                85   90   95

Gln Gly Thr Lys
            100

<210> 463
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 463
Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val
            20   25   30

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ser
        35   40   45

Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly
    50   55   60

Leu Glu Trp Leu Gly Val Ile Trp Ala Ile Gly Ile Thr Asn Tyr Asn
65   70   75   80

Ser Ser Val Lys Gly Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn
85 90 95

Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135

<210> 464
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 464
Gln Val Gln Leu Lys Glu Ser Gly Pro Val Leu Val Ala Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
20 25 30

Asn Ile His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Gln Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

```
Leu Val Thr Val Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Glu Asn Val Leu Thr Gln Ser Pro Ala Ile
    130                 135                 140


Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
145                 150                 155                 160


Ser Ser Val Ser Ser Ser Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly
                165                 170                 175


Ala Ser Pro Lys Val Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly
            180                 185                 190


Val Pro Gly Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
        195                 200                 205


Thr Ile Ser Ser Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
    210                 215                 220


Gln Tyr Ser Gly Tyr Pro Ile Thr Phe Gly Ala Gly Thr Lys Val Glu
225                 230                 235                 240


Val Lys Arg



<210> 465
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 465
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15
```

```
Thr Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ala Ser Tyr
            20                  25                  30

Asn Ile His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
    50                  55                  60

Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Phe Leu
65                  70                  75                  80

Lys Met Ser Ser Leu Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys Arg Ser Asp Asp Tyr Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Glu Asn Gln Met Thr Gln Ser Pro Ser Ser Leu
    130                 135                 140

Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Arg Ala Ser Ser
145                 150                 155                 160

Ser Val Ser Ser Ser Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly Lys
                165                 170                 175

Ala Pro Lys Val Trp Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220
```

Tyr Ser Gly Tyr Pro Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225 230 235 240

Lys Arg

<210> 466
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 466
Met Ala Val Leu Gly Leu Leu Phe Cys Leu Val Thr Phe Pro Ser Cys
1 5 10 15

Val Leu Ser Gln Val Gln Val Lys Glu Ser Gly Pro Phe Leu Val Pro
20 25 30

Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu
35 40 45

Thr Thr Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
50 55 60

Glu Trp Leu Gly Ala Ile Trp Gly Asp Gly Thr Thr Asn Tyr His Ser
65 70 75 80

Ala Leu Ile Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln
85 90 95

Val Phe Leu Lys Leu Asn Ser Leu Gln Thr Asp Asp Thr Ala Thr Tyr
100 105 110

Tyr Cys Ala Lys Leu Gly Asn Tyr Asp Ala Leu Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

```
Gly Ser Gly Gly Gly Gly Ser Asp Val Leu Met Thr Gln Thr Pro Leu
145                 150                 155                 160


Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser
                165                 170                 175


Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr
            180                 185                 190


Leu Gln Lys Pro Gly Gln Ser Pro Asn Leu Leu Ile Tyr Phe Val Ser
        195                 200                 205


Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly
225                 230                 235                 240


Val Tyr Tyr Cys Phe Gln Gly Ser His Val Pro Trp Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Leu Glu Ile Lys
            260


<210> 467
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 467
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
```

```
Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Gly Ser Ser Arg Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Met Asp Ala Ser Gly Ser Tyr Phe Asn Phe Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Thr Thr Leu Thr Gln Ser Pro Ser Phe
    130                 135                 140

Leu Ser Ala Phe Val Gly Asp Arg Ile Thr Ile Thr Cys Arg Ala Ser
145                 150                 155                 160

Pro Gly Ile Arg Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220

Tyr Asn Ser Tyr Pro Leu Ser Phe Gly Gly Gly Thr Lys Val Glu Ile
225                 230                 235                 240
```

Lys Arg

<210> 468
<211> 477
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 468
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Cys 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 Asn 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

Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
        195                 200                 205

Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
    210                 215                 220

Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn
225                 230                 235                 240

Arg Gly Ala Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
                245                 250                 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            260                 265                 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        275                 280                 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    290                 295                 300

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305                 310                 315                 320

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                325                 330                 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365
```

```
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385                 390                 395                 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    450                 455                 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210> 469
<211> 291
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      scFV sequence

<400> 469
Met Lys Tyr Leu Leu Pro Thr Ala Ala Ala Gly Leu Leu Leu Leu Ala
1               5                   10                  15

Ala Gln Pro Ala Met Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45
```

```
Phe Thr Phe Arg Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Arg Gly Asp Asn Thr
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Lys Met Thr Ser Asn Ala Phe Ala Phe
        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 Gln Ser Val Leu
145                 150                 155                 160

Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile
                165                 170                 175

Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
            180                 185                 190

Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly
        195                 200                 205

Asn Thr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Phe Lys
    210                 215                 220

Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp
225                 230                 235                 240

Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Trp
                245                 250                 255
```

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala Ala Ala Glu
260 265 270

Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn Gly Ala Ala His His His
275 280 285

His His His
290

<210> 470
<211> 291
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 470
Met Lys Tyr Leu Leu Pro Thr Ala Ala Ala Gly Leu Leu Leu Leu Ala
1 5 10 15

Ala Gln Pro Ala Met Ala Gln Val Gln Leu Val Gln Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile
65 70 75 80

Gly Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Ala Lys Gln Trp Leu
115 120 125

```
Glu Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn
145                 150                 155                 160

Phe Met Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr
                165                 170                 175

Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
            180                 185                 190

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly
        195                 200                 205

Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr
    210                 215                 220

Ser Gly Asn Ser Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp
225                 230                 235                 240

Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Trp
                245                 250                 255

Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala Glu
            260                 265                 270

Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn Gly Ala Ala His His His
        275                 280                 285

His His His
    290
```

<210> 471
<211> 665
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 471
Met Thr Val Leu Ala Pro Ala Trp Ser Pro Thr Thr Tyr Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Ser Ser Gly Leu Ser Gly Thr Gln Asp Cys Ser Phe
20 25 30

Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu
35 40 45

Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu
50 55 60

Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp Arg Leu Val Leu Ala Gln
65 70 75 80

Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly
85 90 95

Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala
100 105 110

Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser
115 120 125

Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp
130 135 140

Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro
145 150 155 160

Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala
165 170 175

Thr Ala Pro Thr Ala Pro Glu Pro Lys Ser Cys Asp Lys Thr His Thr
180 185 190

```
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
        195                 200                 205

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    210                 215                 220

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
225                 230                 235                 240

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
                245                 250                 255

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            260                 265                 270

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
        275                 280                 285

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    290                 295                 300

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
305                 310                 315                 320

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
                325                 330                 335

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            340                 345                 350

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        355                 360                 365

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    370                 375                 380

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
385                 390                 395                 400
```

```
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Glu Val
                405                 410                 415

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
            420                 425                 430

Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile
        435                 440                 445

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg
    450                 455                 460

Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly
465                 470                 475                 480

Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln
                485                 490                 495

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg
            500                 505                 510

Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
        515                 520                 525

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Gly Gly
    530                 535                 540

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
545                 550                 555                 560

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                565                 570                 575

Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp
            580                 585                 590

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala
        595                 600                 605
```

Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser
610 615 620

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
625 630 635 640

Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly
645 650 655

Gln Gly Thr Lys Val Glu Ile Lys Arg
660 665

<210> 472
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 472
Met Arg Phe Ser Thr Thr Leu Ala Thr Ala Ala Thr Ala Leu Phe Phe
1 5 10 15

Thr Ala Ser Gln Val Ser Ala Glu Val Gln Leu Val Glu Ser Gly Gly
20 25 30

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
35 40 45

Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro
50 55 60

Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr
65 70 75 80

Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp
85 90 95

Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
100 105 110

```
Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
        115                 120                 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
                165                 170                 175

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val
            180                 185                 190

Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
        195                 200                 205

Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg
    210                 215                 220

Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
225                 230                 235                 240

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr
                245                 250                 255

Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser Gly
            260                 265                 270

His His His His His His
        275
```

<210> 473
<211> 280
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 473
Met Arg Phe Ser Thr Thr Leu Ala Thr Ala Ala Thr Ala Leu Phe Phe
1 5 10 15

Thr Ala Ser Gln Val Ser Ala Gly His His His His His His Ser Gly
20 25 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
35 40 45

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
50 55 60

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
65 70 75 80

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
85 90 95

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
100 105 110

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
115 120 125

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
130 135 140

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
165 170 175

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
180 185 190

```
Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr
        195                 200                 205


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser
    210                 215                 220


Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly
225                 230                 235                 240


Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
                245                 250                 255


Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln
            260                 265                 270


Gly Thr Lys Val Glu Ile Lys Ser
        275                 280


<210> 474
<211> 120
<212> PRT
<213> Homo sapiens

<400> 474
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> 475
<211> 49
<212> PRT
<213> Homo sapiens

<400> 475
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> 476
<211> 111
<212> PRT
<213> Homo sapiens

<400> 476
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 His 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 Ile Val Tyr Ala
65                  70                  75                  80


Ser Leu Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu Ala Arg Asn
                85                  90                  95


Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val Arg Ser
            100                 105                 110


<210> 477
<211> 114
<212> PRT
<213> Homo sapiens

<400> 477
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> 478
<211> 27
<212> PRT
<213> Homo sapiens

<400> 478
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> 479
<211> 42
<212> PRT
<213> Homo sapiens

<400> 479
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> 480
<211> 44
<212> PRT
<213> Homo sapiens

<400> 480
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> 481
<211> 41

<212> PRT
<213> Homo sapiens

<400> 481
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> 482
<211> 43
<212> PRT
<213> Homo sapiens

<400> 482
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> 483
<211> 220
<212> PRT
<213> Homo sapiens

<400> 483
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> 484
<211> 187
<212> PRT
<213> Homo sapiens

<400> 484

```
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> 485
<211> 54
<212> PRT
<213> Homo sapiens

<400> 485

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> 486
<211> 60
<212> PRT
<213> Homo sapiens

<400> 486
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> 487
<211> 35
<212> PRT
<213> Homo sapiens

<400> 487
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> 488
<211> 38
<212> PRT
<213> Homo sapiens

<400> 488
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> 489
<211> 54
<212> PRT
<213> Homo sapiens

<400> 489
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> 490
<211> 42
<212> PRT
<213> Homo sapiens

<400> 490
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> 491
<211> 37
<212> PRT
<213> Homo sapiens

<400> 491
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> 492
<211> 42
<212> PRT
<213> Homo sapiens

<400> 492
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> 493
<211> 42
<212> PRT
<213> Homo sapiens

<400> 493
```

```
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> 494
<211> 225
<212> PRT
<213> Homo sapiens

<400> 494
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> 495
<211> 154
<212> PRT
<213> Homo sapiens

<400> 495
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> 496
<211> 194
<212> PRT
<213> Homo sapiens

<400> 496
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> 497
<211> 47
<212> PRT
<213> Homo sapiens

<400> 497
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> 498
<211> 341
<212> PRT
<213> Homo sapiens

<400> 498
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> 499
<211> 48
<212> PRT
<213> Homo sapiens

<400> 499
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> 500
<211> 6
<212> PRT
<213> Homo sapiens

<400> 500
Phe Ala Ala Tyr Arg Ser
1 5

<210> 501
<211> 68
<212> PRT
<213> Homo sapiens

<400> 501
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> 502
<211> 41
<212> PRT
<213> Homo sapiens

<400> 502
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> 503
<211> 40
<212> PRT
<213> Homo sapiens

<400> 503
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> 504
<211> 106
<212> PRT
<213> Homo sapiens

<400> 504
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> 505
<211> 200
<212> PRT
<213> Homo sapiens

<400> 505
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> 506
<211> 222
<212> PRT
<213> Homo sapiens

<400> 506
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> 507
<211> 188
<212> PRT
<213> Homo sapiens

<400> 507

```
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> 508
<211> 70
<212> PRT
<213> Homo sapiens

<400> 508
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> 509
<211> 108
<212> PRT
<213> Homo sapiens

<400> 509

```
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> 510
<211> 153
<212> PRT
<213> Homo sapiens

<400> 510
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> 511
<211> 151
<212> PRT
<213> Homo sapiens

<400> 511
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> 512
<211> 171
<212> PRT
<213> Homo sapiens

<400> 512
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> 513
<211> 127
<212> PRT
<213> Homo sapiens

<400> 513

```
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> 514
<211> 21
<212> PRT
<213> Homo sapiens

<400> 514
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> 515
<211> 171
<212> PRT
<213> Homo sapiens

<400> 515
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> 516
<211> 127
<212> PRT
<213> Homo sapiens

<400> 516
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> 517
<211> 207
```

<212> PRT
<213> Homo sapiens

<400> 517

```
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> 518
<211> 21
<212> PRT
<213> Homo sapiens

<400> 518
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> 519
<211> 182
<212> PRT
<213> Homo sapiens

<400> 519
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> 520
<211> 21
<212> PRT
<213> Homo sapiens

<400> 520
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> 521
<211> 164
<212> PRT
<213> Homo sapiens

<400> 521
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> 522
<211> 21
<212> PRT
<213> Homo sapiens

<400> 522

```
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> 523
<211> 112
<212> PRT
<213> Homo sapiens

<400> 523

```
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> 524
<211> 21
<212> PRT
<213> Homo sapiens

<400> 524
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> 525
<211> 112
<212> PRT
<213> Homo sapiens

<400> 525
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> 526
<211> 113
<212> PRT
<213> Homo sapiens

<400> 526

```
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> 527
<211> 114
<212> PRT
<213> Homo sapiens

<400> 527
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> 528
<211> 98
<212> PRT
<213> Homo sapiens

<400> 528
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> 529
<211> 112
<212> PRT
<213> Homo sapiens

<400> 529
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> 530
<211> 173
<212> PRT
<213> Homo sapiens

<400> 530
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 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> 531
<211> 113
<212> PRT
<213> Homo sapiens

<400> 531
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> 532
<211> 60
<212> PRT
<213> Homo sapiens
```

<400> 532
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> 533
<211> 114
<212> PRT
<213> Homo sapiens

<400> 533
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> 534
<211> 113
<212> PRT
<213> Homo sapiens

<400> 534
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> 535
<211> 22
<212> PRT
<213> Homo sapiens

<400> 535
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> 536
<211> 112
<212> PRT
<213> Homo sapiens

<400> 536
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> 537
<211> 110
<212> PRT
<213> Homo sapiens

<400> 537
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> 538
<211> 137
<212> PRT
<213> Homo sapiens

<400> 538

```
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> 539
<211> 163
<212> PRT
<213> Homo sapiens

<400> 539
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> 540
<211> 38
<212> PRT
<213> Homo sapiens

<400> 540
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> 541
<211> 226
<212> PRT
<213> Homo sapiens

<400> 541
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> 542
<211> 188
<212> PRT
<213> Homo sapiens

<400> 542
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> 543
<211> 21
<212> PRT
<213> Homo sapiens

<400> 543
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> 544
<211> 84
<212> PRT
<213> Homo sapiens

<400> 544
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> 545
<211> 84
<212> PRT
<213> Homo sapiens

<400> 545
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> 546
<211> 47
<212> PRT
<213> Homo sapiens

<400> 546
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> 547
<211> 41
<212> PRT
<213> Homo sapiens

<400> 547
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> 548
<211> 47
<212> PRT
<213> Homo sapiens

<400> 548
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> 549
<211> 20
<212> PRT
<213> Homo sapiens

<400> 549
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> 550
<211> 113
<212> PRT
<213> Homo sapiens

<400> 550
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> 551
<211> 112
<212> PRT
<213> Homo sapiens

<400> 551
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> 552
<211> 102
<212> PRT
<213> Homo sapiens

<400> 552
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> 553
<211> 101
<212> PRT
<213> Homo sapiens

<400> 553
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> 554
<211> 113
<212> PRT
<213> Homo sapiens

<400> 554
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> 555
<211> 112
```

<212> PRT
<213> Homo sapiens

<400> 555
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> 556
<211> 102
<212> PRT
<213> Homo sapiens

<400> 556
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> 557
<211> 101
<212> PRT
<213> Homo sapiens

<400> 557
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> 558
<211> 21
<212> PRT
<213> Homo sapiens
```

<400> 558
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> 559
<211> 49
<212> PRT
<213> Homo sapiens

<400> 559
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> 560
<211> 35
<212> PRT
<213> Homo sapiens

<400> 560
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> 561
<211> 39

<212> PRT
<213> Homo sapiens

<400> 561
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> 562
<211> 149
<212> PRT
<213> Homo sapiens

<400> 562
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> 563
<211> 619
<212> PRT
<213> Homo sapiens

<400> 563
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> 564
<211> 180
<212> PRT
<213> Homo sapiens

<400> 564
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> 565
<211> 240
<212> PRT
<213> Homo sapiens

<400> 565

```
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> 566
<211> 86
<212> PRT
<213> Homo sapiens

<400> 566
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> 567
<211> 21
<212> PRT
<213> Homo sapiens

<400> 567
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> 568
<211> 66
<212> PRT
<213> Homo sapiens

<400> 568
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> 569
<211> 40
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 569
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> 570
<211> 67
<212> PRT
<213> Homo sapiens

<400> 570
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 Arg
65

<210> 571
<211> 84
<212> PRT
<213> Homo sapiens

<400> 571

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> 572
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 572
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 Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
65 70 75 80

```
Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
                85                  90                  95

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser
            100                 105                 110

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
        115                 120                 125

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
    130                 135                 140

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
145                 150                 155                 160

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
                165                 170                 175

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
            180                 185                 190

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
        195                 200                 205

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    210                 215


<210> 573
<211> 283
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 573
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 Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
                85                  90                  95

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
            100                 105                 110

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
        115                 120                 125

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
    130                 135                 140

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
145                 150                 155                 160

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
                165                 170                 175

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
            180                 185                 190

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
        195                 200                 205

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
    210                 215                 220
```

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
225 230 235 240

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
245 250 255

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
260 265 270

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
275 280

<210> 574
<211> 46
<212> PRT
<213> Homo sapiens

<400> 574
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> 575
<211> 31
<212> PRT
<213> Homo sapiens

<400> 575
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> 576
<211> 27
<212> PRT
<213> Homo sapiens

<400> 576
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> 577
<211> 26
<212> PRT
<213> Homo sapiens

<400> 577
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> 578
<211> 363
<212> PRT
<213> Homo sapiens

<400> 578
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> 579
<211> 21
<212> PRT
<213> Homo sapiens

<400> 579
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> 580
<211> 185
<212> PRT
<213> Homo sapiens

<400> 580
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> 581
<211> 106
<212> PRT
<213> Homo sapiens

<400> 581
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> 582
<211> 27
<212> PRT
<213> Homo sapiens

<400> 582
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> 583
<211> 66
<212> PRT
<213> Homo sapiens

<400> 583
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> 584
<211> 33
<212> PRT
<213> Homo sapiens

<400> 584
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> 585
<211> 68
<212> PRT
<213> Homo sapiens

<400> 585
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> 586
<211> 28
<212> PRT
<213> Homo sapiens

<400> 586
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> 587
<211> 26
<212> PRT
<213> Homo sapiens

<400> 587
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> 588
<211> 28
<212> PRT
<213> Homo sapiens

<400> 588
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> 589
<211> 26
<212> PRT
<213> Homo sapiens

<400> 589
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> 590
<211> 69
<212> PRT
<213> Homo sapiens

<400> 590
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> 591
<211> 180
<212> PRT
<213> Homo sapiens

<400> 591
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> 592
<211> 216
<212> PRT
<213> Homo sapiens

<400> 592

```
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> 593
<211> 140
<212> PRT
<213> Homo sapiens

<400> 593
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> 594
<211> 222
<212> PRT
<213> Homo sapiens

<400> 594

```
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> 595
<211> 23
<212> PRT
<213> Homo sapiens

<400> 595
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> 596
<211> 51
<212> PRT
<213> Homo sapiens

<400> 596
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> 597
<211> 21
<212> PRT
<213> Homo sapiens

<400> 597
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> 598
<211> 25
<212> PRT
<213> Homo sapiens

<400> 598
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> 599
<211> 22

<212> PRT
<213> Homo sapiens

<400> 599
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> 600
<211> 725
<212> PRT
<213> Homo sapiens

<400> 600
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> 601
<211> 23
<212> PRT
<213> Homo sapiens

<400> 601

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> 602
<211> 24
<212> PRT
<213> Homo sapiens

<400> 602
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> 603
<211> 21
<212> PRT
<213> Homo sapiens

<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
20

<210> 604
<211> 286
<212> PRT
<213> Homo sapiens

<400> 604
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> 605
<211> 226
<212> PRT
<213> Homo sapiens

<400> 605
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> 606
<211> 83
<212> PRT
<213> Homo sapiens

<400> 606
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> 607
<211> 22
<212> PRT
<213> Homo sapiens

<400> 607
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> 608
<211> 24
<212> PRT
<213> Homo sapiens

<400> 608
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> 609
<211> 25
<212> PRT
<213> Homo sapiens

<400> 609
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> 610
<211> 25
<212> PRT
<213> Homo sapiens

<400> 610
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> 611
<211> 21
<212> PRT
<213> Homo sapiens

<400> 611
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> 612
<211> 23
<212> PRT
<213> Homo sapiens

<400> 612
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> 613
<211> 23
<212> PRT
<213> Homo sapiens

<400> 613
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> 614
<211> 101
<212> PRT
<213> Homo sapiens

<400> 614
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> 615
<211> 257
<212> PRT
<213> Homo sapiens

<400> 615
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> 616
<211> 54
<212> PRT
<213> Homo sapiens

<400> 616
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> 617
<211> 31
<212> PRT
<213> Homo sapiens

<400> 617
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> 618
<211> 24
<212> PRT
<213> Homo sapiens

<400> 618
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> 619
<211> 113

<212> PRT
<213> Homo sapiens

<400> 619
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> 620
<211> 21
<212> PRT
<213> Homo sapiens

<400> 620
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> 621
<211> 233

<212> PRT
<213> Homo sapiens

<400> 621

```
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> 622
<211> 21
<212> PRT
<213> Homo sapiens

<400> 622
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> 623
<211> 24
<212> PRT
<213> Homo sapiens

<400> 623
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> 624
<211> 24
<212> PRT
<213> Homo sapiens

<400> 624
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> 625
<211> 107
<212> PRT
<213> Homo sapiens

<400> 625
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 Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
65   70   75   80

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
                85   90   95

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            100   105

<210> 626
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 626
Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr
1   5   10   15

Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro
            20   25   30

```
Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu
        35                  40                  45


Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
    50                  55                  60


Arg
65


<210> 627
<211> 69
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 627
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> 628
<211> 5
<212> PRT
<213> Homo sapiens

<400> 628
Asp Lys Thr His Thr
1               5
```

<210> 629
<211> 4
<212> PRT
<213> Homo sapiens

<400> 629
Cys Pro Pro Cys
1

<210> 630
<211> 15
<212> PRT
<213> Homo sapiens

<400> 630
Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
1 5 10 15

<210> 631
<211> 12
<212> PRT
<213> Homo sapiens

<400> 631
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr
1 5 10

<210> 632
<211> 10
<212> PRT
<213> Homo sapiens

<400> 632
Lys Ser Cys Asp Lys Thr His Thr Cys Pro
1 5 10

<210> 633
<211> 7
<212> PRT
<213> Homo sapiens

<400> 633
Lys Cys Cys Val Asp Cys Pro
1 5

<210> 634
<211> 7
<212> PRT
<213> Homo sapiens

<400> 634
Lys Tyr Gly Pro Pro Cys Pro
1 5

<210> 635
<211> 16
<212> PRT
<213> Homo sapiens

<400> 635
Val Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 636
<211> 16
<212> PRT
<213> Homo sapiens

<400> 636
Leu Asp Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 637
<211> 39
<212> PRT
<213> Homo sapiens

<400> 637
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> 638
<211> 12
<212> PRT
<213> Homo sapiens

<400> 638
Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
1   5   10

<210> 639
<211> 45
<212> PRT
<213> Homo sapiens

<400> 639
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> 640
<211> 48
<212> PRT
<213> Homo sapiens

<400> 640
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> 641
<211> 79
<212> PRT
<213> Homo sapiens

<400> 641
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> 642
<211> 51
<212> PRT
<213> Homo sapiens

<400> 642
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> 643
<211> 69
<212> PRT
<213> Homo sapiens

<400> 643
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> 644
<211> 44
<212> PRT
<213> Homo sapiens

<400> 644
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> 645
<211> 47
<212> PRT
<213> Homo sapiens

<400> 645
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> 646
<211> 11
<212> PRT
<213> Homo sapiens

<400> 646
Leu Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1   5   10

<210> 647
<211> 101
<212> PRT
<213> Homo sapiens

<400> 647
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> 648
<211> 16
<212> PRT
<213> Homo sapiens

<400> 648
Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
1   5   10   15

<210> 649
<211> 282

<212> PRT
<213> Homo sapiens

<400> 649

```
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> 650
<211> 246
<212> PRT
<213> Homo sapiens

<400> 650

```
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> 651
<211> 45
<212> PRT
<213> Homo sapiens

<400> 651

```
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> 652
<211> 16
<212> PRT
<213> Homo sapiens

<400> 652
Leu Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 653
<211> 43
<212> PRT
<213> Homo sapiens

<400> 653
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> 654
<211> 16
<212> PRT
<213> Homo sapiens

<400> 654
Glu Leu Lys Thr Pro Leu Gly Asp Thr His Thr Cys Pro Arg Cys Pro
1 5 10 15

<210> 655
<211> 15
<212> PRT
<213> Homo sapiens

<400> 655

Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
1 5 10 15

<210> 656
<211> 12
<212> PRT
<213> Homo sapiens

<400> 656
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 657
<211> 12
<212> PRT
<213> Homo sapiens

<400> 657
Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1 5 10

<210> 658
<211> 229
<212> PRT
<213> Homo sapiens

<400> 658
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> 659
<211> 119
<212> PRT
<213> Homo sapiens

<400> 659
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> 660
<211> 282
<212> PRT
<213> Homo sapiens

<400> 660

```
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> 661
<211> 281

<212> PRT
<213> Homo sapiens

<400> 661

```
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> 662
<211> 283
<212> PRT
<213> Homo sapiens

<400> 662
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> 663
<211> 58

<212> PRT
<213> Homo sapiens

<400> 663
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> 664
<211> 282
<212> PRT
<213> Homo sapiens

<400> 664
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> 665
<211> 282
<212> PRT
<213> Homo sapiens

<400> 665

```
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> 666
<211> 281
<212> PRT
<213> Homo sapiens

<400> 666
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 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> 667
<211> 282
<212> PRT
<213> Homo sapiens

<400> 667

```
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> 668
<211> 234
<212> PRT
<213> Homo sapiens

<400> 668

```
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> 669
<211> 20
<212> PRT
<213> Homo sapiens

<400> 669
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> 670
<211> 233
<212> PRT
<213> Homo sapiens
```

<400> 670
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> 671
<211> 13
<212> PRT
<213> Homo sapiens

<400> 671
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                   10


<210> 672
<211> 231
<212> PRT
<213> Homo sapiens

<400> 672
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> 673
<211> 235
<212> PRT
<213> Homo sapiens

<400> 673
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> 674
<211> 223
<212> PRT
<213> Homo sapiens

<400> 674
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> 675
<211> 235
<212> PRT
<213> Homo sapiens

<400> 675
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> 676
<211> 17
<212> PRT
<213> Homo sapiens

<400> 676
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys
1               5                   10                  15


Pro



<210> 677
<211> 61
<212> PRT
<213> Homo sapiens

<400> 677
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> 678
<211> 230
<212> PRT
<213> Homo sapiens

<400> 678
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> 679
<211> 230
<212> PRT
<213> Homo sapiens

<400> 679
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> 680
<211> 12
<212> PRT
<213> Homo sapiens

<400> 680
Ser Pro Asn Met Val Pro His Ala His His Ala Gln
1               5                   10


<210> 681
<211> 107
<212> PRT
<213> Homo sapiens

<400> 681
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> 682
<211> 129
<212> PRT
<213> Homo sapiens

<400> 682

```
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> 683
<211> 229
<212> PRT
<213> Homo sapiens

<400> 683

```
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> 684
<211> 229
<212> PRT
<213> Homo sapiens

<400> 684

```
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> 685
<211> 36
<212> PRT
<213> Homo sapiens

<400> 685

```
Gly Ala Ala Thr Cys Thr Ala Ala Gly Thr Ala Cys Gly Gly Ala Cys
1               5                   10                  15
```

Cys Gly Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Cys Thr Thr Gly
            20   25   30

Cys Cys Cys Thr
        35

<210> 686
<211> 12
<212> PRT
<213> Homo sapiens

<400> 686
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1   5   10

<210> 687
<211> 9
<212> PRT
<213> Homo sapiens

<400> 687
Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1   5

<210> 688
<211> 10
<212> PRT
<213> Homo sapiens

<400> 688
Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1   5   10

<210> 689
<211> 13
<212> PRT
<213> Homo sapiens

<400> 689
Glu Val Val Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1   5   10

<210> 690
<211> 229
<212> PRT
<213> Homo sapiens

<400> 690
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> 691
<211> 22
<212> PRT
<213> Homo sapiens

<400> 691
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> 692
<211> 231
<212> PRT
<213> Homo sapiens

<400> 692
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> 693
<211> 231
<212> PRT
<213> Homo sapiens

<400> 693
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> 694
<211> 236
<212> PRT
<213> Homo sapiens

<400> 694

```
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                  10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser 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 Pro Lys
225 230 235

<210> 695
<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 695
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> 696
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 696
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> 697
<211> 286
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 697
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> 698
<211> 726
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 698
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
20 25 30

Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
35 40 45

Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
50 55 60

Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65 70 75 80

```
Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
                85                  90                  95

Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
            100                 105                 110

Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190

Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285
```

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495
```

```
Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met Tyr
            500                 505                 510

Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His
        515                 520                 525

Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser
    530                 535                 540

Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
545                 550                 555                 560

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys
                565                 570                 575

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
            580                 585                 590

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
        595                 600                 605

Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    610                 615                 620

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
625                 630                 635                 640

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                645                 650                 655

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            660                 665                 670

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        675                 680                 685

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    690                 695                 700
```

```
Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
705                 710                 715                 720


Gln Ala Leu Pro Pro Arg
                725


<210> 699
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 699
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
            20                  25                  30


Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        35                  40                  45


Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
    50                  55                  60


Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65                  70                  75                  80


Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
                85                  90                  95


Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
            100                 105                 110


Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
        115                 120                 125
```

```
Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190

Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Ile
            260                 265                 270

Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
        275                 280                 285

Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
    290                 295                 300

Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val
305                 310                 315                 320

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
                325                 330                 335
```

Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
340 345 350

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
355 360 365

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
370 375 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385 390 395 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
405 410 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 700
<211> 730
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 700
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

```
Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
            20                  25                  30

Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        35                  40                  45

Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65                  70                  75                  80

Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
                85                  90                  95

Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
            100                 105                 110

Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190

Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220
```

```
Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr Pro Ala
            500                 505                 510

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        515                 520                 525

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    530                 535                 540

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
545                 550                 555                 560

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                565                 570                 575

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            580                 585                 590

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        595                 600                 605

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    610                 615                 620

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
625                 630                 635                 640
```

```
Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                645                 650                 655


Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            660                 665                 670


Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        675                 680                 685


Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    690                 695                 700


Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
705                 710                 715                 720


Ala Leu His Met Gln Ala Leu Pro Pro Arg
                725                 730


<210> 701
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 701
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
            20                  25                  30


Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        35                  40                  45


Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
    50                  55                  60
```

```
Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65                  70                  75                  80

Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
                85                  90                  95

Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
            100                 105                 110

Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190

Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala 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 Lys 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> 702
<211> 790
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Chimeric Antigen Receptor

<400> 702
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
20 25 30

Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
35 40 45

Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
50 55 60

Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65 70 75 80

Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
85 90 95

Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
100 105 110

Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145 150 155 160

```
Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190

Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365
```

```
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro Val Phe
            500                 505                 510

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
        515                 520                 525

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
    530                 535                 540

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
545                 550                 555                 560

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
                565                 570                 575
```

```
Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser
            580                 585                 590

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
        595                 600                 605

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
    610                 615                 620

Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg
625                 630                 635                 640

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
                645                 650                 655

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
            660                 665                 670

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        675                 680                 685

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
    690                 695                 700

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
705                 710                 715                 720

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
                725                 730                 735

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
            740                 745                 750

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
        755                 760                 765

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
    770                 775                 780
```

```
Gln Ala Leu Pro Pro Arg
785                 790


<210> 703
<211> 554
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 703
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Asp Val Lys Leu Gln Glu Ser Gly Pro Gly
            20                  25                  30


Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        35                  40                  45


Phe Ser Leu Thr Ser Tyr Ala Val Ser Trp Val Arg Gln Pro Pro Gly
    50                  55                  60


Lys Gly Leu Glu Trp Leu Gly Ile Ile Trp Ser Gly Gly Ala Thr Asn
65                  70                  75                  80


Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
                85                  90                  95


Lys Ser Gln Val Phe Leu Lys Met Asn Gly Leu Gln Thr Asp Asp Thr
            100                 105                 110


Ala Arg Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala Met
        115                 120                 125


Asp Tyr Trp Gly Gln Gly Ala Ser Ile Thr Val Ser Ser Gly Gly Gly
    130                 135                 140
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ile Val Met
145                 150                 155                 160


Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly Asp Gln Ala Ser
                165                 170                 175


Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser Tyr Gly Asn Thr
            180                 185                 190


Tyr Leu Phe Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205


Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220


Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Lys Ile Ser Arg Val Glu
225                 230                 235                 240


Ala Glu Asp Met Gly Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255


Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Phe
            260                 265                 270


Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
        275                 280                 285


Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
    290                 295                 300


Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
305                 310                 315                 320


Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
                325                 330                 335


Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
            340                 345                 350
```

```
Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
        355                 360                 365

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
    370                 375                 380

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val
385                 390                 395                 400

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                405                 410                 415

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            420                 425                 430

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu 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> 704
<211> 728
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 704

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175
```

```
Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240

Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380
```

```
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val
            500                 505                 510

Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile
        515                 520                 525

Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly
    530                 535                 540

Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
545                 550                 555                 560

Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg
                565                 570                 575

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
            580                 585                 590
```

```
Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
        595                 600                 605

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
    610                 615                 620

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
625                 630                 635                 640

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                645                 650                 655

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            660                 665                 670

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        675                 680                 685

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    690                 695                 700

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
705                 710                 715                 720

His Met Gln Ala Leu Pro Pro Arg
                725
```

<210> 705
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 705

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15
```

```
Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220
```

```
Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240

Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            260                 265                 270

Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
        275                 280                 285

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
    290                 295                 300

Phe Pro Gly Pro Ser Lys Pro 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 Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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> 706
<211> 732
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 706
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
85 90 95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
100 105 110

```
Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240

Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320
```

```
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr
            500                 505                 510

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        515                 520                 525
```

```
Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    530                 535                 540

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
545                 550                 555                 560

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                565                 570                 575

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            580                 585                 590

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        595                 600                 605

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    610                 615                 620

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
625                 630                 635                 640

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                645                 650                 655

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            660                 665                 670

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        675                 680                 685

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    690                 695                 700

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
705                 710                 715                 720

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                725                 730
```

<210> 707
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 707
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
85 90 95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
100 105 110

Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
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 Val Gln
145 150 155 160

```
Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240

Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            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
485 490 495

<210> 708
<211> 792
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 708
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
35 40 45

```
Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240

Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255
```

```
Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460
```

```
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro
            500                 505                 510

Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
        515                 520                 525

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
    530                 535                 540

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
545                 550                 555                 560

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
                565                 570                 575

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
            580                 585                 590

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
        595                 600                 605

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
    610                 615                 620

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
625                 630                 635                 640

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                645                 650                 655

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            660                 665                 670
```

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        675   680   685

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    690   695   700

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
705   710   715   720

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                725   730   735

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            740   745   750

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        755   760   765

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    770   775   780

His Met Gln Ala Leu Pro Pro Arg
785   790

<210> 709
<211> 555
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 709
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1   5   10   15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20   25   30

```
Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Thr Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Val Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Ala Val Tyr Phe Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile Ser
            180                 185                 190

Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu
225                 230                 235                 240
```

```
Thr Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro
                245                 250                 255

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            260                 265                 270

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
        275                 280                 285

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
    290                 295                 300

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
305                 310                 315                 320

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
                325                 330                 335

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
            340                 345                 350

His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
        355                 360                 365

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
    370                 375                 380

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
385                 390                 395                 400

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
                405                 410                 415

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
            420                 425                 430

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
        435                 440                 445
```

```
Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
    450                 455                 460

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
465                 470                 475                 480

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
                485                 490                 495

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
            500                 505                 510

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
        515                 520                 525

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
    530                 535                 540

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
545                 550                 555


<210> 710
<211> 725
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 710
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
            20                  25                  30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
    50                  55                  60
```

```
Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
                85                  90                  95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
            100                 105                 110

Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145                 150                 155                 160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180                 185                 190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Cys
            260                 265                 270
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
305                 310                 315                 320

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
                325                 330                 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
    450                 455                 460

Asp Lys Ser Arg Trp Gln Gln 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

Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met Tyr Pro
            500                 505                 510

Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val
        515                 520                 525

Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys
    530                 535                 540

Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
545                 550                 555                 560

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
                565                 570                 575

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
            580                 585                 590

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
        595                 600                 605

Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    610                 615                 620

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
625                 630                 635                 640

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                645                 650                 655

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            660                 665                 670

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
        675                 680                 685
```

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
690 695 700

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
705 710 715 720

Ala Leu Pro Pro Arg
725

<210> 711
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 711
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
20 25 30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
50 55 60

Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65 70 75 80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
85 90 95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
100 105 110

```
Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145                 150                 155                 160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180                 185                 190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Ile Glu
            260                 265                 270

Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr
        275                 280                 285

Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro
    290                 295                 300

Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu
305                 310                 315                 320
```

Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
325 330 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
340 345 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
355 360 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
370 375 380

Ala Asp Ala Pro Ala Tyr Gln 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> 712
<211> 729
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 712
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1   5   10   15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
            20   25   30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
        35   40   45

Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
    50   55   60

Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65   70   75   80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
                85   90   95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
            100   105   110

Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145   150   155   160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165   170   175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180   185   190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195   200   205

```
Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Cys
            260                 265                 270

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
305                 310                 315                 320

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
                325                 330                 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
    450                 455                 460

Asp Lys Ser Arg Trp Gln Gln 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

Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr Pro Ala Pro
            500                 505                 510

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        515                 520                 525

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    530                 535                 540

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
545                 550                 555                 560

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                565                 570                 575

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            580                 585                 590

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
        595                 600                 605

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
    610                 615                 620
```

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
625 630 635 640

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
645 650 655

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
660 665 670

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
675 680 685

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
690 695 700

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
705 710 715 720

Leu His Met Gln Ala Leu Pro Pro Arg
725

<210> 713
<211> 493
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 713
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
20 25 30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
35 40 45

```
Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
    50                  55                  60

Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
                85                  90                  95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
            100                 105                 110

Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145                 150                 155                 160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180                 185                 190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255
```

```
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Ala Ala Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            420                 425                 430

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        435                 440                 445

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    450                 455                 460
```

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
465 470 475 480

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 714
<211> 789
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 714
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
20 25 30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
50 55 60

Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65 70 75 80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
85 90 95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
100 105 110

Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145                 150                 155                 160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180                 185                 190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Glu Pro Lys Ser Cys
            260                 265                 270

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu 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 His
305                 310                 315                 320

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
                325                 330                 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val
    450                 455                 460

Asp Lys Ser Arg Trp Gln Gln 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

Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro Val Phe Leu
            500                 505                 510

Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        515                 520                 525

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    530                 535                 540

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
545                 550                 555                 560
```

```
Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                565                 570                 575

Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys
            580                 585                 590

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
        595                 600                 605

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
    610                 615                 620

Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys
625                 630                 635                 640

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
                645                 650                 655

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
            660                 665                 670

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
        675                 680                 685

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
    690                 695                 700

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
705                 710                 715                 720

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
                725                 730                 735

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
            740                 745                 750

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
        755                 760                 765
```

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
    770   775   780

Ala Leu Pro Pro Arg
785

<210> 715
<211> 553
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 715
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1   5   10   15

Leu Leu Ile Pro Asp Thr Asp Val Gln Leu Gln Glu Ser Gly Pro Val
            20   25   30

Leu Val Lys Thr Gly Ala Ser Val Lys Met Ser Cys Thr Ala Ser Gly
        35   40   45

Tyr Thr Phe Thr Asp His Phe Met Asp Trp Val Lys Gln Ser His Gly
    50   55   60

Lys Ser Leu Glu Trp Ile Gly Ser Leu Asn Pro Tyr Ser Gly Gly Thr
65   70   75   80

Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys
                85   90   95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Asn Ser Leu Thr Ser Val Asp
            100   105   110

Ser Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe 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 Asp Ile Val Met Thr
145                 150                 155                 160

Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly Glu Ser Val Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
            180                 185                 190

Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Arg Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys 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 Phe Ser Val Val Lys
385                 390                 395                 400

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
                405                 410                 415

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
            420                 425                 430

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
        435                 440                 445

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
    450                 455                 460

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
465                 470                 475                 480

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
                485                 490                 495

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
            500                 505                 510

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
        515                 520                 525

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
    530                 535                 540
```

Leu His Met Gln Ala Leu Pro Pro Arg
545 550

<210> 716
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 716
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
50 55 60

His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65 70 75 80

Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
85 90 95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
100 105 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
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 Val Gln
145 150 155 160

```
Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240

Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met Tyr Pro Pro
            500                 505                 510

Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys
        515                 520                 525

Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro
    530                 535                 540

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
545                 550                 555                 560

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
                565                 570                 575
```

```
Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
            580                 585                 590

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
        595                 600                 605

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    610                 615                 620

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
625                 630                 635                 640

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                645                 650                 655

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            660                 665                 670

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        675                 680                 685

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    690                 695                 700

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
705                 710                 715                 720

Leu Pro Pro Arg
```

<210> 717
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 717

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15

Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
    50                  55                  60

His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80

Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205
```

```
Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240

Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Ala Ala Ile Glu Val Met
            260                 265                 270

Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile
        275                 280                 285

His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro
    290                 295                 300

Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys
305                 310                 315                 320

Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val 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 Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415
```

```
Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430


Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445


Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460


Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480


Met Gln Ala Leu Pro Pro Arg
                485


<210> 718
<211> 728
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 718
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30


Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
        35                  40                  45


Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
    50                  55                  60


His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80


Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
                85                  90                  95
```

```
Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240

Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300
```

```
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg
            500                 505                 510
```

```
Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        515                 520                 525

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    530                 535                 540

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
545                 550                 555                 560

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                565                 570                 575

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            580                 585                 590

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        595                 600                 605

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    610                 615                 620

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
625                 630                 635                 640

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                645                 650                 655

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            660                 665                 670

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        675                 680                 685

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    690                 695                 700

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
705                 710                 715                 720
```

His Met Gln Ala Leu Pro Pro Arg
725

<210> 719
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Chimeric Antigen Receptor

<400> 719
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
50 55 60

His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65 70 75 80

Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
85 90 95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
100 105 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
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 Val Gln
145                 150                 155                 160


Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175


Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205


Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220


Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240


Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255


Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Ala Ala 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> 720
<211> 788
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 720
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

```
Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
    50                  55                  60

His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80

Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240
```

```
Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445
```

```
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro Val Phe Leu Pro
            500                 505                 510

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        515                 520                 525

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    530                 535                 540

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
545                 550                 555                 560

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                565                 570                 575

Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys Arg
            580                 585                 590

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
        595                 600                 605

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
    610                 615                 620

Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys
625                 630                 635                 640

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
                645                 650                 655
```

```
Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
            660                 665                 670

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        675                 680                 685

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    690                 695                 700

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
705                 710                 715                 720

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                725                 730                 735

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            740                 745                 750

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        755                 760                 765

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    770                 775                 780

Leu Pro Pro Arg
785
```

<210> 721
<211> 551
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 721

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15
```

```
Leu Leu Ile Pro Asp Thr Ala Leu Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Leu Val Arg Pro Gly Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp Tyr Glu Met His Trp Val Lys Gln Thr Pro Val
    50                  55                  60

His Gly Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80

Ala Tyr Asn Gln Lys Phe Glu Gly Lys Ala Ile Leu Thr Ala Asp Lys
                85                  90                  95

Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
            100                 105                 110

Ser Pro Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        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 Val Gln
145                 150                 155                 160

Met Ile Gln Thr Pro Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val
                165                 170                 175

Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220
```

```
Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile
225                 230                 235                 240


Ala Thr Tyr Phe Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Gly
                245                 250                 255


Gly Gly Thr Lys Leu Glu Ile Asn Arg Ala Ala Ala Phe Val Pro Val
            260                 265                 270


Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
        275                 280                 285


Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
    290                 295                 300


Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
305                 310                 315                 320


Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
                325                 330                 335


Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg
            340                 345                 350


Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
        355                 360                 365


Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
    370                 375                 380


Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly
385                 390                 395                 400


Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
                405                 410                 415


Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
            420                 425                 430
```

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
435 440 445

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
450 455 460

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
465 470 475 480

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
485 490 495

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
500 505 510

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
515 520 525

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
530 535 540

Met Gln Ala Leu Pro Pro Arg
545 550

<210> 722
<211> 728
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 722
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

```
Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
        115                 120                 125

Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190

Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255
```

```
Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460
```

```
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val
            500                 505                 510

Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile
        515                 520                 525

Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly
    530                 535                 540

Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
545                 550                 555                 560

Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg
                565                 570                 575

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
            580                 585                 590

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
        595                 600                 605

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
    610                 615                 620

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
625                 630                 635                 640

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                645                 650                 655

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            660                 665                 670
```

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
675 680 685

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
690 695 700

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
705 710 715 720

His Met Gln Ala Leu Pro Pro Arg
725

<210> 723
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 723
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

```
Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
        115                 120                 125

Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190

Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala
            260                 265                 270

Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        275                 280                 285

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    290                 295                 300
```

```
Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
305                 310                 315                 320

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                325                 330                 335

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            340                 345                 350

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        355                 360                 365

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 724
<211> 732
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 724

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
        115                 120                 125

Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190
```

```
Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400
```

```
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr
            500                 505                 510

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        515                 520                 525

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    530                 535                 540

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
545                 550                 555                 560

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                565                 570                 575

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            580                 585                 590

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        595                 600                 605
```

```
Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    610                 615                 620


Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
625                 630                 635                 640


Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                645                 650                 655


Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            660                 665                 670


Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        675                 680                 685


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    690                 695                 700


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
705                 710                 715                 720


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                725                 730


<210> 725
<211> 496
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 725
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30
```

```
Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
        115                 120                 125

Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190

Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240
```

```
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala
            260                 265                 270

Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
        275                 280                 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
    290                 295                 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
305                 310                 315                 320

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
                325                 330                 335

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
            340                 345                 350

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
        355                 360                 365

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
    370                 375                 380

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
385                 390                 395                 400

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
                405                 410                 415

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
            420                 425                 430

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
        435                 440                 445
```

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
450 455 460

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
465 470 475 480

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 726
<211> 792
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 726
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
115 120 125

```
Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190

Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335
```

```
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro
            500                 505                 510

Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
        515                 520                 525

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
    530                 535                 540
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
545                 550                 555                 560

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
                565                 570                 575

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
            580                 585                 590

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
        595                 600                 605

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
    610                 615                 620

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
625                 630                 635                 640

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                645                 650                 655

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            660                 665                 670

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        675                 680                 685

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    690                 695                 700

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
705                 710                 715                 720

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                725                 730                 735

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            740                 745                 750
```

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        755   760   765

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    770   775   780

His Met Gln Ala Leu Pro Pro Arg
785   790

<210> 727
<211> 556
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 727
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1   5   10   15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20   25   30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35   40   45

Phe Ser Leu Thr Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly
    50   55   60

Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Trp Ser Gly Gly Ala Thr
65   70   75   80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85   90   95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100   105   110

```
Thr Ala Val Tyr Tyr Cys Ala Arg Glu His Tyr Tyr Gly Ser Ser Ala
        115                 120                 125

Met Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Val His Ser Tyr Gly
            180                 185                 190

Asn Thr Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu
        195                 200                 205

Leu Ile Tyr Arg Val Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly Thr His Val Pro
                245                 250                 255

Tyr Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala
            260                 265                 270

Ala Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala
        275                 280                 285

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
    290                 295                 300

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
305                 310                 315                 320
```

```
Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
                325                 330                 335

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
            340                 345                 350

Asn His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
        355                 360                 365

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
    370                 375                 380

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser 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> 728
<211> 728
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 728
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
115 120 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
130 135 140

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
            180                 185                 190

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350
```

```
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val
            500                 505                 510

Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile
        515                 520                 525

Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly
    530                 535                 540

Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala
545                 550                 555                 560
```

```
Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg
                565                 570                 575

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
            580                 585                 590

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
        595                 600                 605

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
    610                 615                 620

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
625                 630                 635                 640

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                645                 650                 655

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            660                 665                 670

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        675                 680                 685

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    690                 695                 700

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
705                 710                 715                 720

His Met Gln Ala Leu Pro Pro Arg
                725
```

<210> 729
<211> 491
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 729
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
115 120 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
165 170 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
180 185 190

```
Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            260                 265                 270

Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
        275                 280                 285

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
    290                 295                 300

Phe Pro Gly Pro Ser Lys Pro 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 Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Gln 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> 730
<211> 732
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 730
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

```
Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        115                 120                 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
            180                 185                 190

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285
```

```
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495
```

```
Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr
            500                 505                 510

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        515                 520                 525

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    530                 535                 540

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
545                 550                 555                 560

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                565                 570                 575

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            580                 585                 590

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        595                 600                 605

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    610                 615                 620

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
625                 630                 635                 640

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                645                 650                 655

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            660                 665                 670

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        675                 680                 685

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    690                 695                 700
```

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
705 710 715 720

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
725 730

<210> 731
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 731
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
115 120 125

```
Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
            180                 185                 190

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            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
485 490 495

<210> 732
<211> 792
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 732
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

```
Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        115                 120                 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
            180                 185                 190

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220
```

```
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro
            260                 265                 270

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    370                 375                 380

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430
```

```
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
465                 470                 475                 480

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495

Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro
            500                 505                 510

Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
        515                 520                 525

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
    530                 535                 540

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
545                 550                 555                 560

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
                565                 570                 575

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
            580                 585                 590

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
        595                 600                 605

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
    610                 615                 620

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
625                 630                 635                 640
```

```
Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                645                 650                 655

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            660                 665                 670

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        675                 680                 685

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    690                 695                 700

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
705                 710                 715                 720

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                725                 730                 735

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            740                 745                 750

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        755                 760                 765

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    770                 775                 780

His Met Gln Ala Leu Pro Pro Arg
785                 790
```

<210> 733
<211> 555
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 733

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Ala Phe Ser Ser Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Val Arg Tyr Tyr Tyr Gly Ser Ser Gly Tyr
        115                 120                 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr Gly Ile
            180                 185                 190

Ser Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205
```

```
Ile Tyr Arg Ala Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
225                 230                 235                 240

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asn Asn Lys Asp Pro Pro
                245                 250                 255

Thr Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala
            260                 265                 270

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
        275                 280                 285

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
    290                 295                 300

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
305                 310                 315                 320

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
                325                 330                 335

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
            340                 345                 350

His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
        355                 360                 365

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
    370                 375                 380

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
385                 390                 395                 400

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
                405                 410                 415
```

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
420 425 430

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
435 440 445

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
450 455 460

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
465 470 475 480

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
485 490 495

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
500 505 510

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
515 520 525

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
530 535 540

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
545 550 555

<210> 734
<211> 726
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 734
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

```
Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125

Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240
```

```
Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445
```

```
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met Tyr
            500                 505                 510

Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His
        515                 520                 525

Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser
    530                 535                 540

Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
545                 550                 555                 560

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys
                565                 570                 575

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
            580                 585                 590

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
        595                 600                 605

Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    610                 615                 620

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
625                 630                 635                 640

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                645                 650                 655
```

```
Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            660                 665                 670


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        675                 680                 685


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    690                 695                 700


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
705                 710                 715                 720


Gln Ala Leu Pro Pro Arg
                725


<210> 735
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 735
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30


Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45


Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80
```

```
Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125

Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Ile
            260                 265                 270

Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
        275                 280                 285
```

```
Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
    290                 295                 300

Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val
305                 310                 315                 320

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
                325                 330                 335

Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
            340                 345                 350

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
        355                 360                 365

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 736
<211> 730
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 736

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15


Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30


Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45


Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80


Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95


Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110


Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125


Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380
```

```
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr Pro Ala
            500                 505                 510

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        515                 520                 525

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    530                 535                 540

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
545                 550                 555                 560

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                565                 570                 575

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            580                 585                 590
```

```
Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        595                 600                 605


Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    610                 615                 620


Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
625                 630                 635                 640


Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                645                 650                 655


Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            660                 665                 670


Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        675                 680                 685


Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    690                 695                 700


Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
705                 710                 715                 720


Ala Leu His Met Gln Ala Leu Pro Pro Arg
                725                 730


<210> 737
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 737
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15
```

```
Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45

Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125

Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220
```

```
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala 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 Lys 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> 738
<211> 790
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 738
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

```
Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125

Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320
```

```
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro Val Phe
            500                 505                 510

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
        515                 520                 525
```

```
Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
    530                 535                 540

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
545                 550                 555                 560

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
                565                 570                 575

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser
            580                 585                 590

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
        595                 600                 605

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
    610                 615                 620

Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg
625                 630                 635                 640

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
                645                 650                 655

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
            660                 665                 670

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        675                 680                 685

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
    690                 695                 700

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
705                 710                 715                 720

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
                725                 730                 735
```

```
Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
            740                 745                 750


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
        755                 760                 765


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
    770                 775                 780


Gln Ala Leu Pro Pro Arg
785                 790


<210> 739
<211> 554
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 739
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                   10                  15


Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30


Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45


Tyr Thr Phe Thr Asp His Phe Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Gln Gly Leu Glu Trp Met Gly Gly Leu Asn Pro Tyr Ser Gly Gly Thr
65                  70                  75                  80


Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95
```

```
Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg His Asn Trp Gly Ala Tyr Phe Asp
        115                 120                 125

Tyr Trp Trp Gly Gln Gly Thr Met 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 Leu
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 Lys Ser Leu Leu His Ser Asn Gly Asn Thr
            180                 185                 190

Tyr Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        195                 200                 205

Tyr Tyr Met Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Met Gln Gly Leu Glu Asp Pro Tyr Thr
                245                 250                 255

Phe Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Phe
            260                 265                 270

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
        275                 280                 285

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
    290                 295                 300
```

```
Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
305                 310                 315                 320

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
                325                 330                 335

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
            340                 345                 350

Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
        355                 360                 365

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
    370                 375                 380

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val
385                 390                 395                 400

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                405                 410                 415

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            420                 425                 430

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu 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> 740
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 740
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
115 120 125

```
Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335
```

```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met Tyr Pro Pro
            500                 505                 510

Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys
        515                 520                 525

Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro
    530                 535                 540
```

```
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
545                 550                 555                 560

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
                565                 570                 575

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
            580                 585                 590

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
        595                 600                 605

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    610                 615                 620

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
625                 630                 635                 640

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                645                 650                 655

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            660                 665                 670

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        675                 680                 685

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    690                 695                 700

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
705                 710                 715                 720

Leu Pro Pro Arg
```

<210> 741
<211> 487

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 741

```
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1               5                  10                  15


Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20                  25                  30


Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45


Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80


Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95


Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110


Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        115                 120                 125


Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160


Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175
```

```
Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Ile Glu Val Met
            260                 265                 270

Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile
        275                 280                 285

His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro
    290                 295                 300

Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys
305                 310                 315                 320

Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val 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 Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380
```

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg
485

<210> 742
<211> 728
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 742
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

```
Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85                  90                  95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        115                 120                 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270
```

```
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480
```

```
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg
            500                 505                 510

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        515                 520                 525

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    530                 535                 540

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
545                 550                 555                 560

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                565                 570                 575

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            580                 585                 590

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        595                 600                 605

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    610                 615                 620

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
625                 630                 635                 640

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                645                 650                 655

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            660                 665                 670

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        675                 680                 685
```

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
690 695 700

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
705 710 715 720

His Met Gln Ala Leu Pro Pro Arg
725

<210> 743
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 743
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

```
Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        115                 120                 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala 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> 744
<211> 788
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 744
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1   5   10   15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
            20   25   30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35   40   45

Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
    50   55   60

Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65   70   75   80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
                85   90   95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100   105   110

Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
        115   120   125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145   150   155   160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165   170   175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
            180   185   190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195   200   205

```
Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
385                 390                 395                 400

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415
```

```
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
465                 470                 475                 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                485                 490                 495

Gly Lys Lys Asp Pro Lys Ala Ala Ala Phe Val Pro Val Phe Leu Pro
            500                 505                 510

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        515                 520                 525

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    530                 535                 540

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
545                 550                 555                 560

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                565                 570                 575

Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys Arg
            580                 585                 590

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
        595                 600                 605

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
    610                 615                 620
```

```
Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys
625                 630                 635                 640

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
                645                 650                 655

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
            660                 665                 670

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        675                 680                 685

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    690                 695                 700

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
705                 710                 715                 720

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                725                 730                 735

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            740                 745                 750

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        755                 760                 765

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    770                 775                 780

Leu Pro Pro Arg
785
```

<210> 745
<211> 551
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 745
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
35 40 45

Tyr Thr Phe Thr Asp Tyr Glu Ile Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Gln Gly Leu Glu Trp Met Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr
65 70 75 80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu
85 90 95

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Arg Arg Arg Tyr Tyr Gly Ser Ser Ser
115 120 125

Phe Asp Tyr Trp Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg
165 170 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr Ala Trp
180 185 190

```
Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Thr
        195                 200                 205

Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln Gly Ser Ala Leu Pro Pro Thr Phe Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Phe Val Pro Val
            260                 265                 270

Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
        275                 280                 285

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
    290                 295                 300

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
305                 310                 315                 320

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
                325                 330                 335

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg
            340                 345                 350

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
        355                 360                 365

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
    370                 375                 380

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly
385                 390                 395                 400
```

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
405 410 415

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
420 425 430

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
435 440 445

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
450 455 460

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
465 470 475 480

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
485 490 495

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
500 505 510

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
515 520 525

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
530 535 540

Met Gln Ala Leu Pro Pro Arg
545 550

<210> 746
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 746
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 Val Gln Leu Gln Gln Ser Gly Pro Gly
            20                  25                  30

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
        35                  40                  45

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
    50                  55                  60

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
65                  70                  75                  80

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn
                85                  90                  95

Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
            100                 105                 110

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp
        115                 120                 125

Leu Glu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
145                 150                 155                 160

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
                165                 170                 175

Ser Gln Thr Ile Trp Ser Tyr Leu Asn Trp Tyr Gln Gln Arg Pro Gly
            180                 185                 190

Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly
        195                 200                 205

Val Pro Ser Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
```

```
Thr Ile Ser Ser Leu Gln Ala Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
225                 230                 235                 240

Gln Ser Tyr Ser Ile Pro Gln Thr Phe Gly Gln Gly Thr Lys Leu Glu
                245                 250                 255

Ile Lys Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            260                 265                 270

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        275                 280                 285

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
    290                 295                 300

Cys Asp Ile Tyr Ile 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> 747
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 747
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 Val Gln Leu Gln Gln Ser Gly Pro Gly
            20                  25                  30


Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
        35                  40                  45


Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
    50                  55                  60


Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
65                  70                  75                  80


Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn
                85                  90                  95
```

```
Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
            100                 105                 110

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp
        115                 120                 125

Leu Glu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
145                 150                 155                 160

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
                165                 170                 175

Ser Gln Thr Ile Trp Ser Tyr Leu Asn Trp Tyr Gln Gln Arg Pro Gly
            180                 185                 190

Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly
        195                 200                 205

Val Pro Ser Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220

Thr Ile Ser Ser Leu Gln Ala Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
225                 230                 235                 240

Gln Ser Tyr Ser Ile Pro Gln Thr Phe Gly Gln Gly Thr Lys Leu Glu
                245                 250                 255

Ile Lys Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp
            260                 265                 270

Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu
        275                 280                 285

Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu
    290                 295                 300
```

Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val
305 310 315 320

Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His
325 330 335

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
340 345 350

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
355 360 365

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
370 375 380

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
385 390 395 400

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
405 410 415

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
420 425 430

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
435 440 445

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
450 455 460

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
465 470 475 480

<210> 748
<211> 544
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 748
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 Val Gln Leu Gln Gln Ser Gly Pro Gly
            20   25   30

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
        35   40   45

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
    50   55   60

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
65   70   75   80

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn
                85   90   95

Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
            100   105   110

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp
        115   120   125

Leu Glu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val
    130   135   140

Ser Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
145   150   155   160

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
                165   170   175

Ser Gln Thr Ile Trp Ser Tyr Leu Asn Trp Tyr Gln Gln Arg Pro Gly
            180   185   190

Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly
        195   200   205

```
Val Pro Ser Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220

Thr Ile Ser Ser Leu Gln Ala Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
225                 230                 235                 240

Gln Ser Tyr Ser Ile Pro Gln Thr Phe Gly Gln Gly Thr Lys Leu Glu
                245                 250                 255

Ile Lys Ala Ala Ala Phe Val Pro Val Phe Leu Pro Ala Lys 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 Asn His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu
            340                 345                 350

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
        355                 360                 365

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
    370                 375                 380

Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
385                 390                 395                 400

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
                405                 410                 415
```

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
420 425 430

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
435 440 445

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
450 455 460

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
465 470 475 480

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
485 490 495

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
500 505 510

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
515 520 525

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
530 535 540

<210> 749
<211> 727
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 749
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
20 25 30

```
Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
        35                  40                  45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
    50                  55                  60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65                  70                  75                  80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
                85                  90                  95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
            100                 105                 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Thr His
        115                 120                 125

Trp Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240
```

```
Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495

Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met
            500                 505                 510

Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile
        515                 520                 525

His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro
    530                 535                 540

Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys
545                 550                 555                 560

Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser
                565                 570                 575

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
            580                 585                 590

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
        595                 600                 605

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
    610                 615                 620

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
625                 630                 635                 640

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                645                 650                 655
```

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
660 665 670

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
675 680 685

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
690 695 700

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
705 710 715 720

Met Gln Ala Leu Pro Pro Arg
725

<210> 750
<211> 792
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 750
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
20 25 30

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
35 40 45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
50 55 60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65 70 75 80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
85 90 95

```
Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
            100                 105                 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Thr His
        115                 120                 125

Trp Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300
```

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495

Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ala Phe Val Pro
            500                 505                 510
```

```
Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
        515                 520                 525

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
    530                 535                 540

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
545                 550                 555                 560

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
                565                 570                 575

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
            580                 585                 590

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
        595                 600                 605

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
    610                 615                 620

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
625                 630                 635                 640

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                645                 650                 655

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            660                 665                 670

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        675                 680                 685

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    690                 695                 700

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
705                 710                 715                 720
```

```
Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                725                 730                 735


Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            740                 745                 750


Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        755                 760                 765


Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    770                 775                 780


His Met Gln Ala Leu Pro Pro Arg
785                 790


<210> 751
<211> 506
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 751
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
            20                  25                  30


Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
        35                  40                  45


Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
    50                  55                  60


Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65                  70                  75                  80
```

```
Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
                85                  90                  95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
            100                 105                 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Thr His
        115                 120                 125

Trp Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Lys Thr Thr
            260                 265                 270

Pro Pro Ser Val Tyr Gly Arg Val Lys Asp Pro Lys Ala Ala Ala Ile
        275                 280                 285
```

```
Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
    290                 295                 300

Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
305                 310                 315                 320

Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val
                325                 330                 335

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
            340                 345                 350

Val 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> 752
<211> 571
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Chimeric Antigen Receptor

<400> 752
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
20 25 30

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
35 40 45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
50 55 60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65 70 75 80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
85 90 95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
100 105 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Thr His
115 120 125

Trp Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
130 135 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

```
Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Lys Thr Thr
            260                 265                 270

Pro Pro Ser Val Tyr Gly Arg Val Lys Asp Pro Lys Ala Ala Ala Ala
        275                 280                 285

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
    290                 295                 300

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
305                 310                 315                 320

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
                325                 330                 335

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
            340                 345                 350

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
        355                 360                 365
```

```
His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
    370                 375                 380

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
385                 390                 395                 400

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
                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
                565                 570
```

<210> 753
<211> 727
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 753
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
20 25 30

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
35 40 45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
50 55 60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65 70 75 80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
85 90 95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
100 105 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Ser Ser
115 120 125

Tyr Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
130 135 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

```
Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365
```

```
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495

Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Val Met
            500                 505                 510

Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile
        515                 520                 525

His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro
    530                 535                 540

Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys
545                 550                 555                 560

Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser
                565                 570                 575
```

```
Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
            580                 585                 590

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
        595                 600                 605

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
    610                 615                 620

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
625                 630                 635                 640

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                645                 650                 655

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            660                 665                 670

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        675                 680                 685

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    690                 695                 700

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
705                 710                 715                 720

Met Gln Ala Leu Pro Pro Arg
                725
```

<210> 754
<211> 792
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 754

```
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
            20                  25                  30

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
        35                  40                  45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
    50                  55                  60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65                  70                  75                  80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
                85                  90                  95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
            100                 105                 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Ser Ser
        115                 120                 125

Tyr Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205

Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220
```

```
Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430
```

```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495

Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala Ala Ala Ala Phe Val Pro
            500                 505                 510

Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
        515                 520                 525

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
    530                 535                 540

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
545                 550                 555                 560

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
                565                 570                 575

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn
            580                 585                 590

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
        595                 600                 605

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
    610                 615                 620

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg
625                 630                 635                 640
```

```
Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                645                 650                 655

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            660                 665                 670

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        675                 680                 685

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    690                 695                 700

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
705                 710                 715                 720

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                725                 730                 735

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            740                 745                 750

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        755                 760                 765

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    770                 775                 780

His Met Gln Ala Leu Pro Pro Arg
785                 790
```

<210> 755
<211> 511
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 755

```
Met Val 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 Thr Glu Val Gln Leu Val Glu Ser Gly
            20                  25                  30

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
        35                  40                  45

Ser Gly Phe Ala Phe Ser Ile Tyr Asp Met Ser Trp Val Arg Gln Thr
    50                  55                  60

Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly
65                  70                  75                  80

Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
                85                  90                  95

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu
            100                 105                 110

Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Ser Gly Tyr Gly Thr His
        115                 120                 125

Trp Gly Val Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
                165                 170                 175

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu
        195                 200                 205
```

```
Ile Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu
225                 230                 235                 240

Gln Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ala Lys Thr Thr
            260                 265                 270

Pro Pro Ser Val Tyr Gly Arg Val Lys Asp Pro Lys Ala Ala Ala Ala
        275                 280                 285

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
    290                 295                 300

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
305                 310                 315                 320

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
                325                 330                 335

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
            340                 345                 350

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
        355                 360                 365

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
    370                 375                 380

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
385                 390                 395                 400

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
                405                 410                 415
```

```
Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
            420                 425                 430

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
        435                 440                 445

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
    450                 455                 460

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
465                 470                 475                 480

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
                485                 490                 495

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            500                 505                 510
```

<210> 756
<211> 703
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 756

```
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 Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Gly Ser Gly Arg Tyr Ala Leu Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
    130                 135                 140

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
    210                 215                 220

Arg Ser Asn Trp Pro Pro Ser Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Arg Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
                245                 250                 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            260                 265                 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        275                 280                 285
```

```
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    290                 295                 300

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305                 310                 315                 320

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                325                 330                 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385                 390                 395                 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    450                 455                 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Asp Pro
465                 470                 475                 480

Lys Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn
                485                 490                 495
```

```
Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys
            500                 505                 510

Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val
        515                 520                 525

Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
    530                 535                 540

Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser
545                 550                 555                 560

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
                565                 570                 575

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg
            580                 585                 590

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
        595                 600                 605

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
    610                 615                 620

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
625                 630                 635                 640

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
                645                 650                 655

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
            660                 665                 670

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
        675                 680                 685

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    690                 695                 700
```

<210> 757
<211> 714
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 757
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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

```
Gly Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg
            180                 185                 190

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro Thr Trp Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Pro Lys Ser Cys Asp Lys
                245                 250                 255

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365
```

```
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys Lys Asp Pro Lys Ala Ala Ala Ile Glu Gly Ala Ala Ala Ala Ile
                485                 490                 495

Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
            500                 505                 510

Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
        515                 520                 525

Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val
    530                 535                 540

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
545                 550                 555                 560

Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
                565                 570                 575
```

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
580 585 590

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
595 600 605

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
610 615 620

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
625 630 635 640

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
645 650 655

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
660 665 670

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
675 680 685

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
690 695 700

Ala Leu His Met Gln Ala Leu Pro Pro Arg
705 710

<210> 758
<211> 701
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 758
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
20 25 30

```
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
    130                 135                 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Val Gly Gly Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn
    210                 215                 220

Asn Trp Pro Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240
```

```
Lys Arg Ala Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
    370                 375                 380

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445
```

```
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Lys Asp Pro Lys Ala
465                 470                 475                 480

Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys
                485                 490                 495

Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser
            500                 505                 510

Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val
        515                 520                 525

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
    530                 535                 540

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
545                 550                 555                 560

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
                565                 570                 575

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
            580                 585                 590

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
        595                 600                 605

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
    610                 615                 620

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
625                 630                 635                 640

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
                645                 650                 655
```

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
660 665 670

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
675 680 685

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
690 695 700

<210> 759
<211> 466
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 759
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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gly Gly Ser Gly Arg Tyr Ala Leu Asp Ile Trp Gly Gln Gly
100 105 110

```
Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
    130                 135                 140

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
    210                 215                 220

Arg Ser Asn Trp Pro Pro Ser Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Arg Ala 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 Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
        355                 360                 365

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
    370                 375                 380

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
385                 390                 395                 400

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
                405                 410                 415

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
            420                 425                 430

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
        435                 440                 445

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
    450                 455                 460

Pro Arg
465
```

<210> 760
<211> 470
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 760

```
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 Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gly Gly Ser Gly Arg Tyr Ala Leu Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
    130                 135                 140

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
    210                 215                 220
```

```
Arg Ser Asn Trp Pro Pro Ser Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Arg Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro
                245                 250                 255

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
            260                 265                 270

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
        275                 280                 285

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
    290                 295                 300

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
305                 310                 315                 320

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
                325                 330                 335

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
            340                 345                 350

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        355                 360                 365

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
    370                 375                 380

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
385                 390                 395                 400

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
                405                 410                 415

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
            420                 425                 430
```

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
        435   440   445

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
    450   455   460

Gln Ala Leu Pro Pro Arg
465   470

<210> 761
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 761
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 Gly Thr Phe Ser Ser Tyr
            20   25   30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Thr Gly Gly Ser Gly Arg Tyr Ala Leu Asp Ile Trp Gly Gln Gly
            100   105   110

```
Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr
    130                 135                 140

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
    210                 215                 220

Arg Ser Asn Trp Pro Pro Ser Tyr Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Arg Ala Ala Ala Phe Val Pro Val Phe Leu Pro Ala Lys
                245                 250                 255

Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
            260                 265                 270

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
        275                 280                 285

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
    290                 295                 300

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
305                 310                 315                 320
```

```
Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys Arg Ser Arg
                325                 330                 335

Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro
            340                 345                 350

Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala
        355                 360                 365

Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu
    370                 375                 380

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
385                 390                 395                 400

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
                405                 410                 415

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
            420                 425                 430

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
        435                 440                 445

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
    450                 455                 460

Gly Lys Pro 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> 762
<211> 470
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Chimeric Antigen Receptor

<400> 762
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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

```
Gly Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg
            180                 185                 190

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro Thr Trp Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Ile Glu Val Met Tyr
                245                 250                 255

Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His
            260                 265                 270

Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser
        275                 280                 285

Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
    290                 295                 300

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys
305                 310                 315                 320

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
                325                 330                 335

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
            340                 345                 350

Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        355                 360                 365
```

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
370 375 380

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
385 390 395 400

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
405 410 415

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
420 425 430

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
435 440 445

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
450 455 460

Gln Ala Leu Pro Pro Arg
465 470

<210> 763
<211> 474
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 763
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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

```
Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Gly Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg
            180                 185                 190

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro Thr Trp Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Thr Thr Thr Pro Ala
                245                 250                 255
```

```
Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            260                 265                 270

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
        275                 280                 285

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
    290                 295                 300

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
305                 310                 315                 320

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                325                 330                 335

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            340                 345                 350

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
        355                 360                 365

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
    370                 375                 380

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
385                 390                 395                 400

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                405                 410                 415

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            420                 425                 430

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        435                 440                 445

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    450                 455                 460
```

Ala Leu His Met Gln Ala Leu Pro Pro Arg
465 470

<210> 764
<211> 534
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 764
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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ala Gly Gly Ser Gly Ser Tyr Tyr Pro Leu Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

```
Gly Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg
            180                 185                 190

Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro Thr Trp Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys Arg Ala Ala Ala Phe Val Pro Val Phe
                245                 250                 255

Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            260                 265                 270

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        275                 280                 285

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
    290                 295                 300

Cys Asp Ile Tyr Ile 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 Asn His Arg Asn 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 Arg Phe Ser Val Val Lys Arg Gly Arg
    370                 375                 380

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
385                 390                 395                 400

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
                405                 410                 415

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
            420                 425                 430

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
        435                 440                 445

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
    450                 455                 460

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
465                 470                 475                 480

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
                485                 490                 495

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
            500                 505                 510

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
        515                 520                 525

Gln Ala Leu Pro Pro Arg
    530
```

<210> 765
<211> 464
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 765
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
130 135 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145 150 155 160

Val Gly Gly Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
165 170 175

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
180 185 190

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn
    210                 215                 220

Asn Trp Pro Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys Arg Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp
                245                 250                 255

Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu
            260                 265                 270

Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu
        275                 280                 285

Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val
    290                 295                 300

Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His
305                 310                 315                 320

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
                325                 330                 335

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            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

<210> 766
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 766
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

```
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
    130                 135                 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Val Gly Gly Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn
    210                 215                 220

Asn Trp Pro Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys Arg Ala Ala Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
                245                 250                 255

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
            260                 265                 270

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
        275                 280                 285

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
    290                 295                 300

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
305                 310                 315                 320
```

```
Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
                325                 330                 335

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
            340                 345                 350

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        355                 360                 365

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    370                 375                 380

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
385                 390                 395                 400

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                405                 410                 415

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            420                 425                 430

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        435                 440                 445

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    450                 455                 460

Leu Pro Pro Arg
465
```

<210> 767
<211> 528
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 767

```
Gln Val Gln Leu Val 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 Gly Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Gly Ile Ile Pro Ile Leu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Trp Gly Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
    130                 135                 140


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160


Val Gly Gly Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175


Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205
```

```
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn
    210                 215                 220

Asn Trp Pro Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys Arg Ala Ala Ala Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr
                245                 250                 255

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
            260                 265                 270

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
        275                 280                 285

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
    290                 295                 300

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
305                 310                 315                 320

Thr Leu Tyr Cys Asn His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu
                325                 330                 335

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
            340                 345                 350

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
        355                 360                 365

Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
    370                 375                 380

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
385                 390                 395                 400

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
                405                 410                 415
```

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
420 425 430

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
435 440 445

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
450 455 460

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
465 470 475 480

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
485 490 495

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
500 505 510

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
515 520 525

<210> 768
<211> 223
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Chimeric Antigen Receptor

<400> 768
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 Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
65                  70                  75                  80

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
                85                  90                  95

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
            100                 105                 110

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
        115                 120                 125

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
    130                 135                 140

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
145                 150                 155                 160

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
                165                 170                 175

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
            180                 185                 190

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
        195                 200                 205

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    210                 215                 220


<210> 769
<211> 496
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Chimeric Antigen Receptor

<400> 769
```

```
Met Val Ala Thr Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro
1               5                  10                  15

His Pro Ala Phe Leu Leu Ile Pro Asp Thr Glu Val Gln Leu Val Glu
            20                  25                  30

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
        35                  40                  45

Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe Gly Met His Trp Val Arg
    50                  55                  60

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Tyr Ile Ser Ser Asp
65                  70                  75                  80

Ser Ser Ala Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile
                85                  90                  95

Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu
            100                 105                 110

Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys Gly Arg Gly Arg Glu Asn
        115                 120                 125

Ile Tyr Tyr Gly Ser Arg Leu Asp Tyr Trp Gly Gln Gly Thr Thr Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala
                165                 170                 175

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val
            180                 185                 190

Asp Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
        195                 200                 205
```

```
Ala Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
225                 230                 235                 240

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Asn
                245                 250                 255

Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Ala Ala
            260                 265                 270

Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
        275                 280                 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
    290                 295                 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
305                 310                 315                 320

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
                325                 330                 335

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
            340                 345                 350

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
        355                 360                 365

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
    370                 375                 380

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
385                 390                 395                 400

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
                405                 410                 415
```

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
420 425 430

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
435 440 445

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
450 455 460

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
465 470 475 480

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 770
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic scFV sequence

<400> 770
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Met Ser Leu Gly
1 5 10 15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Ser Val Ile
20 25 30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser Cys Leu Gln Ser Arg
85 90 95

```
Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys
        115                 120                 125

Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly
    130                 135                 140

Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
145                 150                 155                 160

Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp
                165                 170                 175

Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp
            180                 185                 190

Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala
        195                 200                 205

Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe
    210                 215                 220

Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
225                 230                 235                 240

Ser Val Thr Val Ser Ser
                245
```

<210> 771
<211> 69
<212> PRT
<213> Homo sapiens

<400> 771

```
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> 772
<211> 112
<212> PRT
<213> Homo sapiens

<400> 772
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> 773
<211> 42
```

<212> PRT
<213> Homo sapiens

<400> 773
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> 774
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 774
ggcggcggcg gctctggagg aggaggcagc ggcggaggag gctcc 45

<210> 775
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 775
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
20 25 30

Ala Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu
35 40 45

Ser Val Ser Val Ile Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys

```
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65                  70                  75                  80

Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser
            100                 105                 110

Cys Leu Gln Ser Arg Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly
    130                 135                 140

Glu Gly Ser Thr Lys Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
145                 150                 155                 160

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
                165                 170                 175

Tyr Thr Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly
            180                 185                 190

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro
        195                 200                 205

Ala Tyr Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr
    210                 215                 220

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp
225                 230                 235                 240

Thr Ala Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala
```

```
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
```

465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 776
<211> 599
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 776
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
20 25 30

Ala Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu
35 40 45

Ser Val Ser Val Ile Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65 70 75 80

Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser
100 105 110

Cys Leu Gln Ser Arg Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys
115 120 125

Leu Glu Ile Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly
130 135 140

```
Glu Gly Ser Thr Lys Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
145                 150                 155                 160

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
                165                 170                 175

Tyr Thr Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly
            180                 185                 190

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro
        195                 200                 205

Ala Tyr Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr
    210                 215                 220

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp
225                 230                 235                 240

Thr Ala Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350
```

```
Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Ser Gly Gly Val Gln Val
                485                 490                 495

Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln
            500                 505                 510

Thr Cys Val Val His Tyr Thr Gly Met Leu Gly Asp Gly Lys Lys Val
        515                 520                 525

Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met Leu Gly Lys
    530                 535                 540

Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln Met Ser Val
545                 550                 555                 560
```

Gly Gln Gly Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala
565 570 575

Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu Val Phe Asp
580 585 590

Val Glu Leu Leu Glu Leu Glu
595

<210> 777
<211> 650
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 777
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
20 25 30

Ala Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu
35 40 45

Ser Val Ser Val Ile Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65 70 75 80

Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser
100 105 110

Cys Leu Gln Ser Arg Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys

```
        115                 120                 125

Leu Glu Ile Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly
    130                 135                 140

Glu Gly Ser Thr Lys Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
145                 150                 155                 160

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
                165                 170                 175

Tyr Thr Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly
            180                 185                 190

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro
        195                 200                 205

Ala Tyr Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr
    210                 215                 220

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp
225                 230                 235                 240

Thr Ala Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
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                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Ser Gly Ile Ser Leu Ile
                485                 490                 495

Ala Ala Leu Ala Val Asp Tyr Val Ile Gly Met Glu Asn Ala Met Pro
            500                 505                 510

Trp Asn Leu Pro Ala Asp Leu Ala Trp Phe Lys Arg Asn Thr Leu Asn
        515                 520                 525

Lys Pro Val Ile Met Gly Arg His Thr Trp Glu Ser Ile Gly Arg Pro
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530 535 540

Leu Pro Gly Arg Lys Asn Ile Ile Leu Ser Ser Gln Pro Gly Thr Asp
545 550 555 560

Asp Arg Val Thr Trp Val Lys Ser Val Asp Glu Ala Ile Ala Ala Cys
565 570 575

Gly Asp Val Pro Glu Ile Met Val Ile Gly Gly Gly Arg Val Ile Glu
580 585 590

Gln Phe Leu Pro Lys Ala Gln Lys Leu Tyr Leu Thr His Ile Asp Ala
595 600 605

Glu Val Glu Gly Asp Thr His Phe Pro Asp Tyr Glu Pro Asp Asp Trp
610 615 620

Glu Ser Val Phe Ser Glu Phe His Asp Ala Asp Ala Gln Asn Ser His
625 630 635 640

Ser Tyr Cys Phe Glu Ile Leu Glu Arg Arg
645 650

<210> 778
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 778
Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala
1 5 10 15

Phe Leu Leu Ile Pro
20

<210> 779
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 779
Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
1 5 10 15

Leu Leu Ile Pro Asp Thr
20

<210> 780
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Signal Sequence

<400> 780
Met Val 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 Thr
20

<210> 781
<211> 30
<212> PRT
<213> Homo sapiens

<400> 781
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> 782
<211> 90
<212> DNA
<213> Homo sapiens

<400> 782
atggccccgc ggcgggcgcg cggctgccgg accctcggtc tcccggcgct gctactgctg 60

ctgctgctcc ggccgccggc gacgcggggc 90

<210> 783
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 783
Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

<210> 784
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 784
gctactaact tcagcctgct gaagcaggct ggagacgtgg aggagaaccc tggacct 57

<210> 785
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 785
Ser Gly Glu Ser Arg Arg Val Arg Arg Asn Lys Arg Ser Lys
1 5 10

<210> 786

<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 786
agtggtgagt ccaggagagt gcggcgcaac aagaggagca ag 42

<210> 787
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 787
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 Tyr Pro Tyr Asp Val Pro
20 25 30

Asp Tyr Ala
35

<210> 788
<211> 105
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 788
tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 60

ggtggaggca gcttgcaata cccatacgat gttccagatt acgct 105

<210> 789
<211> 8
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 789
Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 790
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 790
gactacaaag acgatgacga caag 24

<210> 791
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 791
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> 792
<211> 102
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 792
tctggtggcg ggagtggagg aggtgggtcc ggaggggggag ggagcggtgg tggaggttcc 60

ggcgggggggg gtagtggagg cggagggtca ggtgggggca gc 102

<210> 793
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 793
Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ser Gly Gly
20 25 30

Gly Ser

<210> 794
<211> 102
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 794
agtggtggcg ggtccggcgg tggtggtagc gggggtggag gctcaggtgg cggtggcagt 60

tatccttacg atgtgcccga ctatgcttca ggcgggggga gt 102

<210> 795
<211> 22
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 795
Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 796
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 796
ggttcaggag ctactaactt cagcctgctg aagcaggctg gagacgtgga ggagaaccct 60

ggacct 66

<210> 797
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 797
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> 798
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 798
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> 799
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 799
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> 800
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 800
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> 801
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 801
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> 802
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 802
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> 803
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 803
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> 804
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 804
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> 805
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 805
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> 806
<211> 561
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 806
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> 807
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 807
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> 808
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 808
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> 809
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 809
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> 810
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 810
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> 811
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

Destabilizing Domain (DD)

<400> 811
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> 812
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 812
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> 813
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 813
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> 814
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 814
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

ccaggatacc caggtgttct ctctgatgtc caggaggaga aaggctttaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 815
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 815
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> 816
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 816
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> 817
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 817
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> 818
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 818
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> 819
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 819
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> 820
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 820
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> 821
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 821
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> 822
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 822
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> 823
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 823
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> 824
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 824
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 gtttttccca gaaattgatt tggagagata taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc caggaggaga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatga t 561

<210> 825
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 825
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 gtttttttcca gaaattgatt tggagaaata taaacttctg 480

ccagaatacc caggtgttct ctctgacgtc caggagggga aaggcattaa gtacaaattt 540

gaagtatatg agaagaatgg t 561

<210> 826
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 826

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> 827
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 827
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> 828
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 828
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> 829
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 829
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> 830
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 830
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> 831
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 831
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 gttttttcca gaagttgact tggagaaata tagacttcta 480

ccagaatacc caggtgttct ctctgatgtc caggggggaga aaggcattaa gtacaaattt 540

gaagcatata ggaagaatga t 561

<210> 832
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 832
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 gcttttttcca ggaatcgact tggggaaacg taaacttctg 480

ccagaatacc caggtgttct ctctgatgtc cgggaggaga aaggcattaa gtacaaactt 540

gaagtatgtg ggaataat 558

<210> 833

<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 833
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccaga 60

cccgacatcg tgctgacaca gagccctgca tccctggcaa tgtccctggg caagagggca 120

accatctctt gcagggcctc tgagagcgtg tccgtgatcg gcgcccacct gatccactgg 180

taccagcaga agccaggaca gccacctaag ctgctgatct atctggcctc caacctggag 240

acaggagtgc ctgcacggtt ctctggcagc ggctccggca ccgactttac actgaccatc 300

gatccagtgg aggaggacga tgtggccatc tactcttgcc tgcagagcag aatcttcccc 360

aggacatttg gcggcggcac caagctggag atcaagggct ctacaagcgg ctccggcaag 420

cctggctccg gagagggctc taccaaggga cagatccagc tggtgcagtc cggacccgag 480

ctgaagaagc ctggcgagac agtgaagatc agctgtaagg cctccggcta cacattcacc 540

gattattcta tcaactgggt gaagagggca ccaggcaagg gcctgaagtg gatgggctgg 600

atcaatacag agacacggga gcccgcctac gcctatgact tcagaggcag gttcgccttt 660

agcctggaga catctgccag caccgcctac ctgcagatca acaatctgaa gtacgaggat 720

acagccacct atttttgcgc cctggactac agctatgcca tggattattg gggccagggc 780

acatccgtga ccgtgagctc caccacaacc ccagcaccta gaccaccaac accagcaccc 840

accatcgcct ctcagccact gagcctgcgc cccgaggcat gtaggcctgc agcaggcggc 900

gccgtgcaca ccaggggcct ggactttgcc tgcgatatct acatctgggc accactggca 960

ggaacatgtg gcgtgctgct gctgtccctg gtcatcaccc tgtactgcaa gcgcggccgg 1020

aagaagctgc tgtatatctt caagcagccc ttcatgcggc ccgtgcagac aacccaggag 1080

gaggacggct gcagctgtag gttccctgag gaggaggagg gcggctgtga gctgagagtg 1140

aagttttcca ggtctgccga tgccccagcc tacaagcagg gccagaatca gctgtataac 1200

gagctgaatc tgggccggag agaggagtac gacgtgctgg ataagaggag gggacgggac 1260

cccgagatgg gaggcaagcc acggagaaag aacccccagg agggcctgta caatgagctg 1320

cagaaggaca agatggccga ggcctattct gagatcggca tgaagggaga gaggcgccgg 1380

ggcaagggac acgatggcct gtaccagggc ctgagcacag ccaccaagga cacctatgat 1440

gcactgcaca tgcaggccct gcctccaagg tga 1473

<210> 834
<211> 1800
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 834
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccaga 60

cccgacatcg tgctgacaca gagccctgca tccctggcaa tgtccctggg caagagggca 120

accatctctt gcagggcctc tgagagcgtg tccgtgatcg gcgcccacct gatccactgg 180

taccagcaga agccaggaca gccacctaag ctgctgatct atctggcctc caacctggag 240

acaggagtgc ctgcacggtt ctctggcagc ggctccggca ccgactttac actgaccatc 300

gatccagtgg aggaggacga tgtggccatc tactcttgcc tgcagagcag aatcttcccc 360

aggacatttg gcggcggcac caagctggag atcaagggct ctacaagcgg ctccggcaag 420

cctggctccg gagagggctc taccaaggga cagatccagc tggtgcagtc cggacccgag 480

ctgaagaagc ctggcgagac agtgaagatc agctgtaagg cctccggcta cacattcacc 540

gattattcta tcaactgggt gaagagggca ccaggcaagg gcctgaagtg gatgggctgg 600

atcaatacag agacacggga gcccgcctac gcctatgact tcagaggcag gttcgccttt 660

agcctggaga catctgccag caccgcctac ctgcagatca acaatctgaa gtacgaggat 720

acagccacct atttttgcgc cctggactac agctatgcca tggattattg gggccagggc 780

acatccgtga ccgtgagctc caccacaacc ccagcaccta gaccaccaac accagcaccc 840

accatcgcct ctcagccact gagcctgcgc cccgaggcat gtaggcctgc agcaggcggc 900

gccgtgcaca ccaggggcct ggactttgcc tgcgatatct acatctgggc accactggca 960

ggaacatgtg gcgtgctgct gctgtccctg gtcatcaccc tgtactgcaa gcgcggccgg 1020

aagaagctgc tgtatatctt caagcagccc ttcatgcggc ccgtgcagac aacccaggag 1080

gaggacggct gcagctgtag gttccctgag gaggaggagg gcggctgtga gctgagagtg 1140

aagttttcca ggtctgccga tgccccagcc tacaagcagg gccagaatca gctgtataac 1200

gagctgaatc tgggccggag agaggagtac gacgtgctgg ataagaggag gggacgggac 1260

cccgagatgg gaggcaagcc acggagaaag aacccccagg agggcctgta caatgagctg 1320

cagaaggaca agatggccga ggcctattct gagatcggca tgaagggaga gaggcgccgg 1380

ggcaagggac acgatggcct gtaccagggc ctgagcacag ccaccaagga cacctatgat 1440

gcactgcaca tgcaggccct gcctccaagg tctggcggcg tgcaggtgga gacaatcagc 1500

ccaggcgacg gaaggacatt cccaaagagg ggacagacct gcgtggtgca ctacacaggc 1560

atgctgggcg atggcaagaa ggtggacagc tcccgggata gaaacaagcc cttcaagttt 1620

atgctgggca agcaggaagt gatcagggga tgggaggagg gagtggcaca gatgtccgtg 1680

ggacagggcg ccaagctgac catctctcct gactacgcct atggagcaac aggacaccca 1740

ggaatcatcc cacctcacgc caccctggtg tttgatgtgg agctgctgga gctggagtga 1800

<210> 835
<211> 1953
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 835
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccaga 60

cccgacatcg tgctgacaca gagccctgca tccctggcaa tgtccctggg caagagggca 120

accatctctt gcagggcctc tgagagcgtg tccgtgatcg gcgcccacct gatccactgg 180

taccagcaga agccaggaca gccacctaag ctgctgatct atctggcctc caacctggag 240

acaggagtgc ctgcacggtt ctctggcagc ggctccggca ccgactttac actgaccatc 300

gatccagtgg aggaggacga tgtggccatc tactcttgcc tgcagagcag aatcttcccc 360

aggacatttg gcggcggcac caagctggag atcaagggct ctacaagcgg ctccggcaag 420

cctggctccg gagagggctc taccaaggga cagatccagc tggtgcagtc cggacccgag 480

ctgaagaagc ctggcgagac agtgaagatc agctgtaagg cctccggcta cacattcacc 540

gattattcta tcaactgggt gaagagggca ccaggcaagg gcctgaagtg gatgggctgg 600

atcaatacag agacacggga gcccgcctac gcctatgact tcagaggcag gttcgccttt 660

agcctggaga catctgccag caccgcctac ctgcagatca acaatctgaa gtacgaggat 720

acagccacct atttttgcgc cctggactac agctatgcca tggattattg gggccagggc 780

acatccgtga ccgtgagctc caccacaacc ccagcaccta gaccaccaac accagcaccc 840

accatcgcct ctcagccact gagcctgcgc cccgaggcat gtaggcctgc agcaggcggc 900

gccgtgcaca ccaggggcct ggactttgcc tgcgatatct acatctgggc accactggca 960

ggaacatgtg gcgtgctgct gctgtccctg gtcatcaccc tgtactgcaa gcgcggccgg 1020

aagaagctgc tgtatatctt caagcagccc ttcatgcggc ccgtgcagac aacccaggag 1080

gaggacggct gcagctgtag gttccctgag gaggaggagg gcggctgtga gctgagagtg 1140

aagttttcca ggtctgccga tgccccagcc tacaagcagg gccagaatca gctgtataac 1200

gagctgaatc tgggccggag agaggagtac gacgtgctgg ataagaggag gggacgggac 1260

cccgagatgg gaggcaagcc acggagaaag aacccccagg agggcctgta caatgagctg 1320

cagaaggaca agatggccga ggcctattct gagatcggca tgaagggaga gaggcgccgg 1380

ggcaagggac acgatggcct gtaccagggc ctgagcacag ccaccaagga cacctatgat 1440

gcactgcaca tgcaggccct gcctccaagg tccggaatct ctctgatcgc cgccctggca 1500

gtggactacg tgatcggcat ggagaacgcc atgccatgga atctgcccgc cgatctggcc 1560

tggttcaagc ggaacaccct gaataagcca gtgatcatgg gcagacacac atgggagtct 1620

atcggcaggc ccctgcctgg acgcaagaac atcatcctga gctcccagcc cggcaccgac 1680

gatagggtga catgggtgaa gtccgtggac gaggcaatcg cagcatgcgg cgatgtgccc 1740

gagatcatgg tcatcggcgg cggcagagtg atcgagcagt tcctgcctaa ggcccagaag 1800

ctgtacctga cccacatcga cgccgaggtg gagggcgaca cacactttcc tgattatgag 1860

ccagacgatt gggagagcgt gttctccgag tttcacgacg ccgatgccca gaacagccac 1920

agctattgtt ttgagatcct ggagcggaga tga 1953

<210> 836
<211> 1335
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Promoter sequence

<400> 836
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> 837
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 837
ggaggaggag gcagcggcgg aggaggctcc ggcggcggcg gctct 45

<210> 838
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 838
tcaggtggcg gtagtggtgg gggaggatct ggaggcggag gaagcggggg tggaggttca 60

ggtggaggca gcttgcaa 78

<210> 839
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 839
tccggtggag gtagcggtgg agggggttct ggtggaggag gttctggagg tggaggttct 60

ggcggtgggt ccttgcaa 78

<210> 840
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 840
tctggcggag gaagcggagg cggaggatct ggtggtggtg gatctggcgg cggtggtagt 60

ggcggaggtt ctctgcaa 78

<210> 841
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 841
tccgggggggg gtagcggggg agggggttcc ggcgggggag ggtctggagg gggaggttcc 60

ggcgggggggt ccttgcaa 78

<210> 842
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 842
tctggcggag gatctggagg aggcggatct ggaggaggag gcagtggagg cggaggatct 60

ggcggaggat ctctgcag 78

<210> 843
<211> 78
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 843
tctggcggag gaagcggagg cggaggatct ggtggtggtg gatctggcgg cggtggtagt 60

ggcggaggtt ctctgcaa 78

<210> 844
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 844
sgggsggggs ggggsggggs 20

<210> 845
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 845
agtggtggcg ggtccggcgg tggtggtagc gggggtggag gctcaggtgg cggtggcagt 60

<210> 846
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 846
tctagataat acgactcact agagatcc 28

<210> 847
<211> 16
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 847
tatggccaca accatg 16

<210> 848
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 848
aatctagata atacgactca ctagagatcc 30

<210> 849
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 849
gcttgccaca acccacaagg agacgacctt cc 32

<210> 850
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 850
Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

<210> 851
<211> 57
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Spacer sequence

<400> 851
gcaaccaatt ttagtctact taaacaagca ggtgatgtag aagaaaatcc aggtcca 57

<210> 852
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 852
Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
1 5

<210> 853
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 853
tacccatacg atgttccaga ttacgct 27

<210> 854
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 854
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> 855
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 855

```
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> 856
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 856

```
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> 857
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 857
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> 858
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 858
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> 859
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 859
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> 860
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 860
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> 861
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 861
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> 862
<211> 187
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 862
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> 863
<211> 186
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Destabilizing Domain (DD)

<400> 863
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

<210> 864
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Cleavage site

<400> 864
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> 865
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Cleavage site

<400> 865
ggagctacta acttcagcct gctgaagcag gctggagacg tggaggagaa ccctggacct   60

<210> 866
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      Cleavage site

<400> 866
Asn Pro Gly Pro
1

<210> 867
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      HA Tag

<400> 867
tatccttacg atgtgcccga ctatgct   27

<210> 868
<211> 27

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
HA Tag

<400> 868
tatccgtacg acgtaccaga ctacgca 27

<210> 869
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 869
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> 870
<211> 477
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 870
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> 871
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 871
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> 872
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 872
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> 873
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 873
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> 874
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 874

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> 875
<211> 477
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 875
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> 876
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 876
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> 877
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 877
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> 878
<211> 321
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 878
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> 879
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 879
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> 880
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 880
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> 881
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 881
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> 882
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 882
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> 883
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 883
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> 884
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 884
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> 885

<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 885
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> 886
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 886
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> 887
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

Destabilizing Domain (DD)

<400> 887
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> 888
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 888
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> 889
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 889
ggagtgcagg tggaaaccat ctccccagga gacgggcgca ccttccccaa gcgcggccag 60

acctgcgtgg tgcactacac cgggatgctt ggagatggaa agaaagttga ctcctcccgg 120

gacagaaaca agccctttaa gtttatgcta ggcaagcagg aggtgatccg aggctgggaa 180

gaaggggttg cccagatgag tgtgggtcag ggagccaaac tgactatatc tccagattat 240

gcctatggtg ccactgggca cccaggcatc atcccaccac atgccactct cgtcttcgat 300

gtggagcttc tagaactgga a 321

<210> 890
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 890
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> 891
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 891
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> 892
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 892
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> 893

<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 893
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> 894
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 894
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> 895
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 895
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> 896
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 896
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> 897
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 897
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> 898
<211> 558

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 898
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> 899
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 899
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> 900
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 900
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> 901
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 901
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> 902
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 902
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> 903
<211> 558
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 903
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> 904
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 904
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> 905
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Destabilizing Domain (DD)

<400> 905
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> 906
<211> 686
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 906
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

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Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
145                 150                 155                 160

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp
                165                 170                 175

Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
            180                 185                 190

Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser
        195                 200                 205

Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala
    210                 215                 220
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Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
225                 230                 235                 240

Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Val Trp Gly
                245                 250                 255

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Phe Glu Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Gly Ser 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 Thr Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
            340                 345                 350

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
        355                 360                 365

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
    370                 375                 380

His Met Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
385                 390                 395                 400

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
                405                 410                 415

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
            420                 425                 430
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Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        435                 440                 445

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    450                 455                 460

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465                 470                 475                 480

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                485                 490                 495

Pro Arg Gly Ser Val Gly Ser Leu Asn Cys Ile Val Ala Val Ser Gln
            500                 505                 510

Asn Met Gly Ile Gly Lys Asn Gly Asp Leu Pro Trp Pro Pro Leu Arg
        515                 520                 525

Asn Glu Phe Arg Tyr Phe Gln Arg Met Thr Thr Thr Ser Ser Val Glu
    530                 535                 540

Gly Lys Gln Asn Leu Val Ile Met Gly Lys Lys Thr Trp Phe Ser Ile
545                 550                 555                 560

Pro Glu Lys Asn Arg Pro Leu Lys Gly Arg Ile Asn Leu Val Leu Ser
                565                 570                 575

Arg Glu Leu Lys Glu Pro Pro Gln Gly Ala His Phe Leu Ser Arg Ser
            580                 585                 590

Leu Asp Asp Ala Leu Lys Leu Thr Glu Gln Pro Glu Leu Ala Asn Lys
        595                 600                 605

Val Asp Met Val Trp Ile Val Gly Gly Ser Ser Val Ile Lys Glu Ala
    610                 615                 620

Met Asn His Pro Gly His Leu Lys Leu Phe Val Thr Arg Ile Met Gln
625                 630                 635                 640
```

Asp Phe Glu Ser Asp Thr Phe Phe Pro Glu Ile Asp Leu Glu Lys Tyr
645 650 655

Lys Leu Leu Pro Glu Tyr Pro Gly Val Leu Ser Asp Val Gln Glu Glu
660 665 670

Lys Gly Ile Lys Tyr Lys Phe Glu Val Tyr Glu Lys Asn Asp
675 680 685

<210> 907
<211> 2061
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 907
atgctgctgc tcgtgacatc tctgctgctg tgcgagctgc cccaccccgc ctttctgctg 60

atccccgata tccagatgac ccagtccccg agctccctgt ccgcctctgt gggcgatagg 120

gtcaccatca cctgccgtgc cagtcaggat gtgaatactg ctgtagcctg gtatcaacag 180

aaaccaggaa aagctccgaa actactgatt tactcggcat ccttccttta ttctggagtc 240

ccttctcgct tctctggatc tagatctggg acggatttca ctctgaccat cagcagtctg 300

cagccggaag acttcgcaac ttattactgt cagcaacatt atactactcc tcccacgttc 360

ggacagggta ccaaggtgga gatcaaaggg tctacatctg gatctgggaa gccgggttct 420

ggtgagggtt ctggtgaggt tcagctggtg gagtctggcg gtggcctggt gcagccaggg 480

ggctcactcc gtttgtcctg tgcagcttct ggcttcaaca ttaaagacac ctatatacac 540

tgggtgcgtc aggccccggg taagggcctg gaatgggttg caaggattta tcctacgaat 600

ggttatacta gatatgccga tagcgtcaag ggccgtttca ctataagcgc agacacatcc 660

aaaaacacag cctacctgca gatgaacagc ctgcgtgctg aggacactgc cgtctattat 720

tgttctagat ggggagggga cggcttctat gctatggacg tgtggggtca aggaaccctg 780

gtcaccgtct cctcggctag cttcgaaacc acgacgccag cgccgcgacc accaacaccg 840

gcgcccacca tcgcgtcgca gcccctgtcc ctgcgcccag aggcgtgccg gccagcggcg 900

ggggggcgcag tgcacacgag ggggctggac ttcgcctgtg atggatctat ctacatctgg 960

gcgcccttgg ccgggacttg tggggtcctt ctcctgtcac tggttatcac cctttactgc 1020

actagtaaac ggggcagaaa gaaactcctg tatatattca aacaaccatt tatgagacca 1080

gtacaaacta ctcaagagga agatggctgt agctgccgat ttccagaaga agaagaagga 1140

ggatgtgaac tgcatatgag agtgaagttc agcaggagcg cagacgcccc cgcgtacaag 1200

cagggccaga accagctcta taacgagctc aatctaggac gaagagagga gtacgatgtt 1260

ttggacaaga gacgtggccg ggaccctgag atgggggaa agccgagaag gaagaaccct 1320

caggaaggcc tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt 1380

gggatgaaag gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggtctcagt 1440

acagccacca aggacaccta cgacgccctt cacatgcagg ccctgccccc tcgcggatcc 1500

gttggttcgc taaactgcat cgtcgctgtg tcccagaaca tgggcatcgg caagaacggg 1560

gacctgccct ggccaccgct caggaatgaa ttcagatatt tccagagaat gaccacaacc 1620

tcttcagtag aaggtaaaca gaatctggtg attatgggta agaagacctg gttctccatt 1680

cctgagaaga atcgaccttt aaagggtaga attaatttag ttctcagcag agaactcaag 1740

gaacctccac aaggagctca ttttctttcc agaagtctag atgatgcctt aaaacttact 1800

gaacaaccag aattagcaaa taaagtagac atggtctgga tagttggtgg cagttctgtt 1860

attaaggaag ccatgaatca cccaggccat cttaaactat ttgtgacaag gatcatgcaa 1920

gactttgaaa gtgacacgtt ttttccagaa attgatttgg agaaatataa acttctgcca 1980

gaatacccag gtgttctctc tgatgtccag gaggagaaag gcattaagta caaatttgaa 2040

gtatatgaga agaatgattg a 2061

<210> 908
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 908
Gln Leu Ile Gly Met Leu Gln Gly Leu Met Arg Asp Leu

1 5 10

<210> 909
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 909
cagctgatag ggatgctaca aggcctgatg cgtgacctg 39

<210> 910
<211> 399
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 910
gcgccaacta gtagcagcac aaaaaagaca cagcttcaac tggagcacct gctgctggac 60

ctgcagatga tccttaacgg aatcaacaac tacaagaacc ccaagctgac caggatgctg 120

acgtttaagt tttacatgcc caagaaggcc accgaactca aacacctgca atgcctggag 180

gaagagctga aaccgcttga ggaagtgttg aacctggccc aaagcaagaa tttccacctg 240

aggcccaggg acctgataag caacatcaac gtgatcgtgc tggaactgaa gggtagcgag 300

accaccttca tgtgcgagta cgccgacgag accgcaacca tcgtggagtt cctgaaccga 360

tggataacat tctgccagag catcattagc actctgacc 399

<210> 911
<211> 1293
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 911
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgcccccctc acagctgcaa ctgcctaccc tgccgctcgt catggtggcc 240

cccagcggcg caagactggg cccgttgccg cacctgcaag ccttgctgca ggaccggcca 300

catttcatgc accagctcag caccgtggac gcacatgcaa ggacacccgt gctgcaagtc 360

caccccctgg agagccctgc catgatcagc ctgacgccgc ccaccaccgc aaccggcgtg 420

ttttcactga aggcaagacc cgggctgcca ccgggcatca acgtggccag cctggaatgg 480

gtgagcaggg agccagcgct cctgtgtacc ttcccaaacc catccgcccc aagaaaggac 540

agcaccctgt ctgccgtgcc ccaatcatct tacccgctgc tggcgaatgg cgtatgcaag 600

tggcccggat gtgaaaaggt gttcgaggag ccggaagatt tcctgaaaca ttgccaggcc 660

gaccacctgt tggacgaaaa gggaagggcc caatgcctgc ttcagaggga gatggtgcag 720

agcttggagc aacaactcgt gctcgagaag gagaagctga gcgccatgca ggcacacctc 780

gccggcaaga tggccctgac caaagccagt agcgtagcca gctccgacaa gggtagctgt 840

tgcatcgtgg ccgcaggaag tcaaggcccc gttgtgcccg cctggagcgg tccaagggag 900

gcacccgact cactgttcgc cgtgaggagg catctgtggg gcagccacgg taacagcacg 960

ttccccgagt tcctgcataa catggactac ttcaagttcc acaacatgcg gcctccattc 1020

acctacgcca cactgataag gtgggctatc ctggaggctc ccgagaagca aaggaccctg 1080

aacgagatct accactggtt caccaggatg ttcgctttct ttaggaacca ccccgcgacc 1140

tggaaaaacg ccataaggca taacttgagc cttcacaagt gcttcgtgag ggtggagagt 1200

gagaaaggtg ccgtgtggac tgtggatgag ttggagttcc gcaagaagcg aagccaacga 1260

cctagcaggt gtagcaatcc aacccccgga ccc 1293

<210> 912
<211> 1290
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 912
ccgaacccaa ggccagggaa gccctctgct cctagcctgg ccctcggccc cagccctggc 60

gctagcccct cttggagggc ggctccgaag gcttccgacc tcctgggtgc taggggccct 120

ggtggaacct tccaaggcag ggatctgcga ggaggggcgc acgcctctag ctcaagcctg 180

aacccgatgc ccccctcaca gctgcaactg cctaccctgc cgctcgtcat ggtggccccc 240

agcggcgcaa gactgggccc gttgccgcac ctgcaagcct tgctgcagga ccggccacat 300

ttcatgcacc agctcagcac cgtggacgca catgcaagga cacccgtgct gcaagtccac 360

cccctggaga gccctgccat gatcagcctg acgccgccca ccaccgcaac cggcgtgttt 420

tcactgaagg caagacccgg gctgccaccg ggcatcaacg tggccagcct ggaatgggtg 480

agcagggagc cagcgctcct gtgtaccttc ccaaacccat ccgccccaag aaaggacagc 540

accctgtctg ccgtgcccca atcatcttac ccgctgctgg cgaatggcgt atgcaagtgg 600

cccggatgtg aaaaggtgtt cgaggagccg gaagatttcc tgaaacattg ccaggccgac 660

cacctgttgg acgaaaaggg aagggcccaa tgcctgcttc agagggagat ggtgcagagc 720

ttggagcaac aactcgtgct cgagaaggag aagctgagcg ccatgcaggc acacctcgcc 780

ggcaagatgg ccctgaccaa agccagtagc gtagccagct ccgacaaggg tagctgttgc 840

atcgtggccg caggaagtca aggccccgtt gtgcccgcct ggagcggtcc aagggaggca 900

cccgactcac tgttcgccgt gaggaggcat ctgtggggca gccacggtaa cagcacgttc 960

cccgagttcc tgcataacat ggactacttc aagttccaca acatgcggcc tccattcacc 1020

tacgccacac tgataaggtg ggctatcctg gaggctcccg agaagcaaag gaccctgaac 1080

gagatctacc actggttcac caggatgttc gctttcttta ggaaccaccc cgcgacctgg 1140

aaaaacgcca taaggcataa cttgagcctt cacaagtgct tcgtgagggt ggagagtgag 1200

aaaggtgccg tgtggactgt ggatgagttg gagttccgca agaagcgaag ccaacgacct 1260

agcaggtgta gcaatccaac ccccggaccc 1290

<210> 913
<211> 1188
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 913
atgccgaacc caaggccagg gaagccctct gctcctagcc tggccctcgg ccccagccct 60

ggcgctagcc cctcttggag ggcggctccg aaggcttccg acctcctggg tgctaggggc 120

cctggtggaa ccttccaagg cagggatctg cgaggagggg cgcacgcctc tagctcaagc 180

ctgaacccga tgccccccctc acagctgcag ctcagcaccg tggacgcaca tgcaaggaca 240

cccgtgctgc aagtccaccc cctggagagc cctgccatga tcagcctgac gccgcccacc 300

accgcaaccg gcgtgttttc actgaaggca agacccgggc tgccaccggg catcaacgtg 360

gccagcctgg aatgggtgag cagggagcca gcgctcctgt gtaccttccc aaacccatcc 420

gccccaagaa aggacagcac cctgtctgcc gtgccccaat catcttaccc gctgctggcg 480

aatggcgtat gcaagtggcc cggatgtgaa aaggtgttcg aggagccgga agatttcctg 540

aaacattgcc aggccgacca cctgttggac gaaaagggaa gggcccaatg cctgcttcag 600

agggagatgg tgcagagctt ggagcaacaa ctcgtgctcg agaaggagaa gctgagcgcc 660

atgcaggcac acctcgccgg caagatggcc ctgaccaaag ccagtagcgt agccagctcc 720

gacaagggta gctgttgcat cgtggccgca ggaagtcaag gccccgttgt gcccgcctgg 780

agcggtccaa gggaggcacc cgactcactg ttcgccgtga ggaggcatct gtggggcagc 840

cacggtaaca gcacgttccc cgagttcctg cataacatgg actacttcaa gttccacaac 900

atgcggcctc cattcaccta cgccacactg ataaggtggg ctatcctgga ggctcccgag 960

aagcaaagga ccctgaacga gatctaccac tggttcacca ggatgttcgc tttctttagg 1020

aaccaccccg cgacctggaa aaacgccata aggcataact tgagccttca caagtgcttc 1080

gtgagggtgg agagtgagaa aggtgccgtg tggactgtgg atgagttgga gttccgcaag 1140

aagcgaagcc aacgacctag caggtgtagc aatccaaccc ccggaccc 1188

<210> 914
<211> 1185
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Payload sequence

<400> 914
ccgaacccaa ggccagggaa gccctctgct cctagcctgg ccctcggccc cagccctggc 60

gctagcccct cttggagggc ggctccgaag gcttccgacc tcctgggtgc taggggccct 120

ggtggaacct tccaaggcag ggatctgcga ggaggggcgc acgcctctag ctcaagcctg 180

aacccgatgc ccccctcaca gctgcagctc agcaccgtgg acgcacatgc aaggacaccc 240

gtgctgcaag tccacccccct ggagagccct gccatgatca gcctgacgcc gcccaccacc 300

gcaaccggcg tgttttcact gaaggcaaga cccgggctgc caccgggcat caacgtggcc 360

agcctggaat gggtgagcag ggagccagcg ctcctgtgta ccttcccaaa cccatccgcc 420

ccaagaaagg acagcaccct gtctgccgtg ccccaatcat cttacccgct gctggcgaat 480

ggcgtatgca agtggcccgg atgtgaaaag gtgttcgagg agccggaaga tttcctgaaa 540

cattgccagg ccgaccacct gttggacgaa aagggaaggg cccaatgcct gcttcagagg 600

gagatggtgc agagcttgga gcaacaactc gtgctcgaga aggagaagct gagcgccatg 660

caggcacacc tcgccggcaa gatggccctg accaaagcca gtagcgtagc cagctccgac 720

aagggtagct gttgcatcgt ggccgcagga agtcaaggcc ccgttgtgcc cgcctggagc 780

ggtccaaggg aggcacccga ctcactgttc gccgtgagga ggcatctgtg gggcagccac 840

ggtaacagca cgttccccga gttcctgcat aacatggact acttcaagtt ccacaacatg 900

cggcctccat tcacctacgc cacactgata aggtgggcta tcctggaggc tcccgagaag 960

caaaggaccc tgaacgagat ctaccactgg ttcaccagga tgttcgcttt ctttaggaac 1020

caccccgcga cctggaaaaa cgccataagg cataacttga gccttcacaa gtgcttcgtg 1080

agggtggaga gtgagaaagg tgccgtgtgg actgtggatg agttggagtt ccgcaagaag 1140

cgaagccaac gacctagcag gtgtagcaat ccaacccccg gaccc 1185

<210> 915
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

Leader sequence

<400> 915
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgctgctgca cgcagccaga 60

ccc 63

<210> 916
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
scFV sequence

<400> 916
gacatcgtgc tgacacagag ccctgcatcc ctggcaatgt ccctgggcaa gagggcaacc 60

atctcttgca gggcctctga gagcgtgtcc gtgatcggcg cccacctgat ccactggtac 120

cagcagaagc caggacagcc acctaagctg ctgatctatc tggcctccaa cctggagaca 180

ggagtgcctg cacggttctc tggcagcggc tccggcaccg actttacact gaccatcgat 240

ccagtggagg aggacgatgt ggccatctac tcttgcctgc agagcagaat cttccccagg 300

acatttggcg gcggcaccaa gctggagatc aagggctcta caagcggctc cggcaagcct 360

ggctccggag agggctctac caagggacag atccagctgg tgcagtccgg acccgagctg 420

aagaagcctg gcgagacagt gaagatcagc tgtaaggcct ccggctacac attcaccgat 480

tattctatca actgggtgaa gagggcacca ggcaagggcc tgaagtggat gggctggatc 540

aatacagaga cacgggagcc cgcctacgcc tatgacttca gaggcaggtt cgcctttagc 600

ctggagacat ctgccagcac cgcctacctg cagatcaaca atctgaagta cgaggataca 660

gccacctatt tttgcgccct ggactacagc tatgccatgg attattgggg ccagggcaca 720

tccgtgaccg tgagctcc 738

<210> 917
<211> 207
<212> DNA
<213> Homo sapiens

<400> 917
accacaaccc cagcacctag accaccaaca ccagcaccca ccatcgcctc tcagccactg 60

agcctgcgcc ccgaggcatg taggcctgca gcaggcggcg ccgtgcacac caggggcctg 120

gactttgcct gcgatatcta catctgggca ccactggcag gaacatgtgg cgtgctgctg 180

ctgtccctgg tcatcaccct gtactgc 207

<210> 918
<211> 336
<212> DNA
<213> Homo sapiens

<400> 918
agagtgaagt tttccaggtc tgccgatgcc ccagcctaca agcagggcca gaatcagctg 60

tataacgagc tgaatctggg ccggagagag gagtacgacg tgctggataa gaggagggga 120

cgggaccccg agatgggagg caagccacgg agaaagaacc cccaggaggg cctgtacaat 180

gagctgcaga aggacaagat ggccgaggcc tattctgaga tcggcatgaa gggagagagg 240

cgccggggca agggacacga tggcctgtac cagggcctga gcacagccac caaggacacc 300

tatgatgcac tgcacatgca ggccctgcct ccaagg 336

<210> 919
<211> 126
<212> DNA
<213> Homo sapiens

<400> 919
aagcgcggcc ggaagaagct gctgtatatc ttcaagcagc ccttcatgcg gcccgtgcag 60

acaacccagg aggaggacgg ctgcagctgt aggttccctg aggaggagga gggcggctgt 120

gagctg 126

<210> 920
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 920
Ala Ser Phe Glu
1

<210> 921
<211> 12
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 921
gctagcttcg aa 12

<210> 922
<211> 90
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Leader sequence

<400> 922
atggccccgc ggcgggcgcg cggctgccgg accctcggtc tcccggcgct gctactgctg 60

ctgctgctcc ggccgccggc gacgcggggc 90

<210> 923
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 923
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

```
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Arg 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 His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Gly Glu Val Gln Leu Val
        115                 120                 125

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
    130                 135                 140

Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val
145                 150                 155                 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro
                165                 170                 175

Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
            180                 185                 190

Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser
        195                 200                 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly
    210                 215                 220

Asp Gly Phe Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr
225                 230                 235                 240

Val Ser Ser
```

<210> 924
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 924
gatatccaga tgacccagtc cccgagctcc ctgtccgcct ctgtgggcga tagggtcacc 60

atcacctgcc gtgccagtca ggatgtgaat actgctgtag cctggtatca acagaaacca 120

ggaaaagctc cgaaactact gatttactcg gcatccttcc tttattctgg agtcccttct 180

cgcttctctg gatctagatc tgggacggat ttcactctga ccatcagcag tctgcagccg 240

gaagacttcg caacttatta ctgtcagcaa cattatacta ctcctcccac gttcggacag 300

ggtaccaagg tggagatcaa agggtctaca tctggatctg ggaagccggg ttctggtgag 360

ggttctggtg aggttcagct ggtggagtct ggcggtggcc tggtgcagcc agggggctca 420

ctccgtttgt cctgtgcagc ttctggcttc aacattaaag acacctatat acactgggtg 480

cgtcaggccc cgggtaaggg cctggaatgg gttgcaagga tttatcctac gaatggttat 540

actagatatg ccgatagcgt caagggccgt ttcactataa gcgcagacac atccaaaaac 600

acagcctacc tgcagatgaa cagcctgcgt gctgaggaca ctgccgtcta ttattgttct 660

agatggggag gggacggctt ctatgctatg gacgtgtggg gtcaaggaac cctggtcacc 720

gtctcctcg 729

<210> 925
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Construct

<400> 925
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> 926
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 926
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggggcg cagtgcacac gagggggctg 120

gacttcgcct gtgat 135

<210> 927
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 927
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> 928
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Construct

<400> 928

atctacatct gggcgccctt ggccgggact tgtggggtcc ttctcctgtc actggttatc 60

acccttttact gc 72

<210> 929
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 929
Gly Gly Gly Gly
1

<210> 930
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 930
Gly Gly Gly Gly Gly
1 5

<210> 931
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Linker sequence

<400> 931
Gly Gly Gly Gly Gly Gly Gly Gly
1 5

<210> 932
<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> 932
Asp Xaa Glu Xaa Asn Pro Gly Pro
1 5

<210> 933
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic 6xHis tag

<400> 933
His His His His His His
1 5