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(54) **Title:** SYNTHETIC INTERMEMBRANE PROTEOLYSIS RECEPTORS FOR CUSTOM ANTIGEN-INDUCED TRANSCRIPTIONAL REGULATION

(57) **Abstract:** The present disclosure generally relates to, among other things, a new class of receptors engineered to modulate transcriptional regulation in a ligand-dependent manner. In particular, the new receptors contain a heterologous stop-transfer-sequence and a γ-secretase cleavable transmembrane domain. The disclosure also provides compositions and methods useful for producing such receptors, nucleic acids encoding same, host cells genetically modified with the nucleic acids, as well as methods for modulating an activity of a cell and/or for the treatment of various diseases such as cancers.

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SYNTHETIC INTERMEMBRANE PROTEOLYSIS RECEPTORS FOR CUSTOM ANTIGEN-INDUCED TRANSCRIPTIONAL REGULATION

STATEMENT REGARDING FEDERALLY SPONSORED R&D

[0001] This invention was made with government support under grant no. OD025751 awarded by The National Institutes of Health. The government has certain rights in the invention.

CROSS REFERENCE TO RELATED APPLICATION

[0002] The present application claims priority to U.S. Provisional Patent Application Serial No. 63/164,995 filed on March 23, 2021, the disclosure of which is incorporated by reference herein in its entirety, including any drawings.

INCORPORATION OF THE SEQUENCE LISTING

[0003] This application contains a Sequence Listing, which is hereby incorporated herein by reference in its entirety. The accompanying Sequence Listing text file, named "048536-696001WO_Sequence Listing_ST25.txt" was created on March 18, 2022 and is 307 KB.

FIELD

[0004] The present disclosure relates generally to new synthetic cellular receptors that bind cell-surface ligands and have selectable specificities and activities. The disclosure also provides compositions and methods useful for producing such receptors, nucleic acids encoding same, host cells genetically modified with the nucleic acids, as well as methods for modulating an activity of a cell and/or for the treatment of various diseases such as cancers.

BACKGROUND

[0005] An important problem which limits the development of engineered cell therapies in humans is the ability to regulate therapeutic gene expression and engineered cell activity. For example, the first generation of chimeric antigen receptor T cells (CAR-T) lack the ability to modulate or turn off CAR-T activity when needed; other problems include off-target activity and off-tumor/on-target activity (i.e., wherein the CAR-T target antigen is also found on normal cells outside the tumor). One possible solution to these problems is to use a synthetic receptor that is capable of modifying gene expression and/or cellular behavior. Existing synthetic Notch

(SynNotch) receptors are capable of binding user-defined cell surface displayed ligands, which triggers proteolytic cleavage of the receptor and release of a transcriptional regulator that induces a custom transcriptional program in the cell. In addition, some existing SynNotch receptors do not require the Notch regulatory regions (NRR) thought to necessary for the induced cleavage of the receptor.

[0006] The present disclosure provides, among other things, novel chimeric polypeptides, including a new class of synthetic receptors that do not require sequence from Notch receptors.

SUMMARY

[0007] The present disclosure describes synthetic chimeric polypeptides (*e.g.*, chimeric receptors) that do not require sequence from Notch receptors. In particular, systematic engineering efforts have illustrated that one can utilize (1) a ADAM protease cleavable extracellular domain (*e.g.*, hinge domain from CD8), (2) a γ-secretase cleavable transmembrane domain (TMD), and (3) a stop-transfer-sequence to rationally build synthetic regulated intermembrane proteolysis receptors (SynRIPRs). As described in greater detail below, these receptors can be used to target various therapeutically relevant cell types to sites of disease and regulate the therapeutic activity the cell in a controlled and localized fashion. These receptors can be linked to inducible transcriptional programs such that when the cell senses a disease site it will locally produce therapeutics such as antibodies, cytokines, toxins, and adjuvants. They are a highly versatile and programmable platform for cellular engineering, and essentially the production of any genetically encodable therapeutic can regulated by these receptors.

[0008] Provided in some embodiments of the disclosure are synthetic chimeric receptors that exhibit a range of signal characteristics mediated by inclusion of heterologous STS and TMD sequences. These receptors provide a range of sensitivity, including a receptor that is sensitive to the degree of T-cell activation when it is expressed in an activated T cell. Some embodiments, when expressed in a T-cell, exhibit higher ligand-induced signal levels when the T-cell is activated, as compared to the ligand-induced signal level when the T-cell is not activated.

[0009] In some embodiments, the present disclosure provides, among other things, a new class of chimeric receptors containing a non-Notch transmembrane domain (TMD) including at least one γ-secretase site. It is believed that the modulation of TMD cleavage facilitates the optimization and/or improvement of the activity of the chimeric receptors disclosed herein, which in turn can be particularly useful in modulating cell activity and/or in treating diseases. In some embodiments, the chimeric receptors of the disclosure include non-Notch STS sequences, which allow the chimeric receptors disclosed herein to have a broad range of desired characteristics. For example, by altering the STS as described herein, and selecting different juxtamembrane domains, one can produce receptors having different noise levels (i.e., the basal level of receptor activation in the absence of the selected target ligand), different signal levels (i.e., the expression level obtained in the presence of the selected target ligand), and different signal:noise ratios.

[0010] In one aspect, provided herein are chimeric polypeptides including, from N-terminus to C-terminus: (a) an extracellular binding domain having a binding affinity for a selected ligand; (b) a linking sequence; (c) a transmembrane domain (TMD) having at least about 80% sequence identity to the transmembrane domain of a Type 1 transmembrane receptor and including one or more ligand-inducible proteolytic cleavage sites; and (d) an intracellular domain (ICD) including a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site between the transcriptional regulator and the linking sequence, and wherein the chimeric polypeptide does not include a sequence from a Notch receptor.

[0011] Non-limiting exemplary embodiments of the chimeric polypeptides provided herein include one or more of the following features: in some embodiments, the chimeric polypeptide further includes a stop-transfer sequence (STS) between the TMD and the ICD; in some embodiments, the TMD includes a polypeptide sequence having at least 80% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor and includes a γ-secretase cleavage site; in some embodiments, the TMD includes a polypeptide sequence having at least 90% sequence identity to a transmembrane domain from a Type I transmembrane receptor and includes a γ-secretase cleavage site; in some embodiments, the TMD includes a polypeptide sequence having at least 95% sequence identity to a transmembrane domain from a Type I transmembrane receptor and includes a γ-secretase cleavage site. In some embodiments, the Type 1 transmembrane receptor is selected from the group consisting of CLSTN1, CLSTN2, APLP1, APLP2, LRP8, APP, BTC, TGBR3, SPN, CD44, CSF1R, CXCL16, CX3CL1, DCC, DLL1, DSG2, DAG1, CDH1, EPCAM, EPHA4, EPHB2, EFNB1, EFNB2, ErbB4, GHR, HLA-

A, IFNAR2, IL1R1, IL1R2, IL6R, INSR, ERN1, ERN2, JAG2, KCNE1, KCNE2, KCNE3, KCNE4, KL, CHL1, PTPRF, SCN1B, SCN3B, NPR3, NGFR, PLXDC2, PAM, AGER, ROBO1, SORCS3, SORCS1, SORL1, SORT1, SDC1, SDC2, TYR, TYRP1, DCT, VASN, FLT1, CDH5, PKHD1, NECTIN1, PCDHGC3, NRG1, LRP1B, CDH2, NRG2, PTPRK, SCN2B, Nradd, and PTPRM, and comprises a γ-secretase cleavage site. In some embodiments, the Type 1 transmembrane receptor is APP, CLSTN1, CLSTN2, EPCAM, KCNE3, NECTIN1, PCDHGC3, and PTPRF. In some embodiments, the chimeric polypeptides provided herein include a stop-transfer sequence (STS), and wherein the STS is heterologous to the TMD. In some embodiments, the STS includes a sequence having at least 70% sequence identity to a STS sequence from CSF1R, CXCL16, DAG1, GHR, PTPRF, AGER, KL, NRG1, LRP1B, Jag2, EPCAM, KCNE3, CDH2, NRG2, PTPRK, BTC, EPHA3, IL1R2, PTPRF, or PTPRM. In some embodiments, the STS comprises a sequence having at least 70% sequence identity to a STS sequence from CSF1R, DAG1, AGER, NRG1, KCNE3, PTPRF, or PTPRM.

[0012] In some embodiments, the extracellular domain includes an antigen-binding moiety capable of binding to a ligand on the surface of a cell. In some embodiments, the cell is a pathogenic cell. In some embodiments, the ligand includes a protein or a carbohydrate. In some embodiments, the ligand is selected from the group consisting of CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3d, CD3e, CD3g, CD4, CD5, CD7, CD8a, CD8b, CD19, CD20, CD21, CD22, CD23, CD25, CD27, CD28, CD33, CD34, CD40, CD45, CD48, CD52, CD59, CD66, CD70, CD71, CD72, CD73, CD79A, CD79B, CD80 (B7.1), CD86 (B7.2), CD94, CD95, CD134, CD140 (PDGFR4), CD152, CD154, CD158, CD178, CD181 (CXCR1), CD182 (CXCR2), CD183 (CXCR3), CD210, CD246, CD252, CD253, CD261, CD262, CD273 (PD-L2), CD274 (PD-L1), CD276 (B7H3), CD279, CD295, CD339 (JAG1), CD340 (HER2), EGFR, FGFR2, CEA, AFP, CA125, MUC-1, MAGE, BCMA (CD269), ALPPL2, GFP, eGFP, and SIRPα.

[0013] In some embodiments, the ligand is selected from the group consisting of CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3d, CD3e, CD3g, CD4, CD5, CD7, CD8a, CD8b, CD19, CD20, CD21, CD22, CD23, CD25, CD27, CD28, CD33, CD34, CD40, CD45, CD48, CD52, CD59, CD66, CD70, CD71, CD72, CD73, CD79A, CD79B, CD80 (B7.1), CD86 (B7.2), CD94, CD95, CD134, CD140 (PDGFR4), CD152, CD154, CD158, CD178, CD181 (CXCR1), CD182 (CXCR2), CD183 (CXCR3), CD210, CD246, CD252, CD253, CD261, CD262, CD273 (PD-

L2), CD274 (PD-L1), CD276 (B7H3), CD279, CD295, CD339 (JAG1), CD340 (HER2), EGFR, FGFR2, CEA, AFP, CA125, MUC-1, and MAGE, Alkaline phosphatase, placental-like 2 (ALPPL2), B-cell maturation antigen (BCMA), Green Fluorescent Protein (GFP), Enhanced Green Fluorescent Protein (EGFP), and Signal regulatory protein α (SIRPα).

[0014] In some embodiments, the ligand is selected from cell surface receptors, adhesion proteins, integrins, mucins, lectins, tumor-associated antigens, and tumor-specific antigens. In some embodiments, the ligand is a tumor-associated antigen or a tumor-specific associated antigen. In some embodiments, the extracellular binding domain includes the ligand-binding portion of a receptor. In some embodiments, the antigen-binding moiety is selected from the group consisting of an antibody, a nanobody, a diabody, a triabody, or a minibody, a $F(ab')_2$ fragment, a Fab fragment, a single chain variable fragment (scFv), a single domain antibody (sdAb), or a functional fragment thereof. In some embodiments, the antigen-binding moiety includes an scFv.

[0015] In some embodiments, the antigen-binding moiety is a tumor-associated antigen selected from the group consisting of CD19, B7H3 (CD276), BCMA (CD269), ALPPL2, CD123, CD171, CD179a, CD20, CD213A2, CD22, CD24, CD246, CD272, CD30, CD33, CD38, CD44v6, CD46, CD71, CD97, CEA, CLDN6, CLECL1, CS-1, EGFR, EGFRvIII, ELF2M, EpCAM, EphA2, Ephrin B2, FAP, FLT3, GD2, GD3, GM3, GPRC5D, HER2 (ERBB2/neu), IGLL1, IL-11Ra, KIT (CD117), MUC1, NCAM, PAP, PDGFR-β, PRSS21, PSCA, PSMA, ROR1, SIRPα, SSEA-4, TAG72, TEM1/CD248, TEM7R, TSHR, VEGFR2, ALPI, citrullinated vimentin, cMet, and Axl. In some embodiments, the tumor-associated antigen is CD19, CEA, HER2, MUC1, CD20, BCMA, ALPPL2, or EGFR. In some embodiments, the tumor-associated antigen is CD19.

[0016] In some embodiments, the ligand-inducible proteolytic cleavage site is a γ-secretase cleavage site. In some embodiments, the transcriptional regulator includes a transcriptional activator, or a transcriptional repressor. In some embodiments, the ICD includes a nuclear localization sequence and a transcriptional regulator sequence selected from Gal4-VP16, Gal4-VP64, tetR-VP64, ZFHD1-VP64, Gal4-KRAB, and HAP1-VP16. In some embodiments, the chimeric polypeptides of the disclosure further include a signal sequence, a detectable label, a tumor-specific cleavage site, a disease-specific cleavage site, or a combination thereof.

[0017] In some embodiments, the chimeric polypeptides of the disclosure include an STS with an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 89, 92, 108, 115, 138, 146, or 156.

[0018] In some embodiments, the hinge domain is capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding. In some embodiments, the linking sequence includes an amino acid sequence having at least 80% sequence identity to a hinge domain derived from CD8α hinge domain, a CD28 hinge domain, a CD152 hinge domain, a PD-1 hinge domain, a CTLA4 hinge domain, an OX40 hinge domain, an IgG1 hinge domain, an IgG2 hinge domain, an IgG3 hinge domain, and an IgG4 hinge domain, or a functional variant of any thereof. In some embodiments, the hinge domain is derived from a CD8α hinge domain or a functional variant thereof. In some embodiments, the hinge domain comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 157-161.

[0019] In some embodiments, the TMD includes an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64. In some embodiments, the TMD includes an amino acid sequence having at least 90% sequence identity to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64. In some embodiments, the TMD includes an amino acid sequence having at least 95% sequence identity to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64. In some embodiments, the TMD includes an amino acid sequence substantially identical to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64.

[0020] In some embodiments, the chimeric polypeptides of the disclosure include: (a) a linking sequence including an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 157-161; (b) a TMD including an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NO: 1-84, 178, 182-185, and 190-192; and (c) a STS including an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 85-156 and 173.

[0021] In another aspect, provided herein are nucleic acids including a nucleotide sequence that encodes a chimeric polypeptide as disclosed herein. In some embodiments, the nucleotide sequence is incorporated into an expression cassette or an expression vector. In some embodiments, the expression vector is a viral vector. In some embodiments, the viral vector is a lentiviral vector, an adenovirus vector, an adeno-associated virus vector, or a retroviral vector. In some embodiments, the viral vector is a lentivival vector.

[0022] In another aspect, provided herein are recombinant cells including (a) a chimeric polypeptide as disclosed herein and/or (b) a recombinant nucleic acid as disclosed herein. In some embodiments, the cell is a mammalian cell. In some embodiments, the mammalian cell is an immune cell, a neuron, an epithelial cell, an endothelial cell, or a stem cell. In some embodiments, the immune cell is a B cell, a monocyte, a natural killer cell, a basophil, an eosinophil, a neutrophil, a dendritic cell, a macrophage, a regulatory T cell, a helper T cell, a cytotoxic T cell, or other T cell. In some embodiments, the recombinant cell further includes: (a) a second chimeric polypeptide as disclosed herein; and/or (b) a second nucleic acid as disclosed herein; wherein the first chimeric polypeptide and the second chimeric polypeptide do not have the same sequence, and/or the first nucleic acid or the second nucleic acid do not have the same sequence. In some embodiments, the chimeric polypeptide modulates the expression and/or activity of the second chimeric polypeptide.

[0023] In some embodiments, the recombinant cell of the disclosure further includes an expression cassette encoding a protein of interest operably linked to a promoter, wherein expression of the protein is modulated by the transcriptional regulator encoded by the chimeric receptor. In some embodiments, the protein of interest is heterologous to the cell. In some embodiments, the promoter is GAL4. In some embodiments, the protein of interest is a cytokine, a cytotoxin, a chemokine, an immunomodulator, a pro-apoptotic factor, an anti-apoptotic factor, a hormone, a differentiation factor, a de-differentiation factor, an immune cell receptor, or a reporter.

[0024] In another aspect, further provided herein are cell cultures including at least one recombinant cell as disclosed herein and a culture medium.

[0025] In yet another aspect, provided herein are pharmaceutical compositions including a pharmaceutically acceptable carrier and one or more of the following: (a) a recombinant nucleic acid as disclosed herein, or (b) a recombinant cell as disclosed herein. In some embodiments, the disclosed pharmaceutical composition includes a recombinant nucleic acid as disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, the recombinant nucleic acid is encapsulated in a viral capsid or a lipid nanoparticle (LNP).

[0026] In another aspect, provided herein are methods for modulating an activity of a cell, including: (a) providing a recombinant cell of the disclosure, and (b) contacting it with a selected ligand, wherein binding of the selected ligand to the extracellular binding domain induces cleavage of a ligand-inducible proteolytic cleavage site and releases the transcriptional regulator, wherein the released transcriptional regulator modulates an activity of the recombinant cell. In some embodiments, the contacting is carried out *in vivo*, *ex vivo*, or *in vitro*. In some embodiments, the activity of the cell is selected from the group consisting of: expression of a selected gene of the cell, proliferation of the cell, apoptosis of the cell, non-apoptotic death of the cell, differentiation of the cell, de-differentiation of the cell, migration of the cell, secretion of a molecule from the cell, cellular adhesion of the cell, and cytolytic activity of the cell. In some embodiments, the released transcriptional regulator modulates expression of a gene product of the cell. In some embodiments, the released transcriptional regulator modulates expression of a heterologous gene product. In some embodiments, the gene product of the cell is selected from the group consisting of a chemokine, a chemokine receptor, a chimeric antigen receptor, a cytokine, a cytokine receptor, a differentiation factor, a growth factor, a growth factor receptor, a hormone, a metabolic enzyme, a pathogen derived protein, a proliferation inducer, a receptor, an RNA guided nuclease, a site-specific nuclease, a T cell receptor, a toxin, a toxin-derived protein, a transcriptional regulator, a transcriptional activator, a transcriptional repressor, a translational regulator, a translational activator, a translational repressor, an activating immuno-receptor, an antibody, an apoptosis inhibitor, an apoptosis inducer, an engineered T cell receptor, an immuno-activator, an immuno-inhibitor, and an inhibiting immuno-receptor. In some embodiments, the released transcriptional regulator modulates differentiation of the cell, and wherein the cell is an immune cell, a stem cell, a progenitor cell, or a precursor cell

[0027] Another aspect relates to methods for inhibiting an activity of a target cell in an individual, including administering to the individual an effective number of the recombinant cell of the disclosure, wherein the recombinant cell inhibits an activity of the target cell in the individual. In some embodiments, the target cell is an acute myeloma leukemia cell, an anaplastic lymphoma cell, an astrocytoma cell, a B-cell cancer cell, a breast cancer cell, a colon cancer cell, an ependymoma cell, an esophageal cancer cell, a glioblastoma cell, a glioma cell, a leiomyosarcoma cell, a liposarcoma cell, a liver cancer cell, a lung cancer cell, a mantle cell lymphoma cell, a melanoma cell, a neuroblastoma cell, a non-small cell lung cancer cell, an oligodendroglioma cell, an ovarian cancer cell, a pancreatic cancer cell, a peripheral T-cell lymphoma cell, a renal cancer cell, a sarcoma cell, a stomach cancer cell, a carcinoma cell, a mesothelioma cell, or a sarcoma cell. In some embodiments, the target cell is a pathogenic cell.

[0028] In another aspect, provided herein are methods for treating a disease in an individual, the methods including a step of administering to the individual an effective number of the recombinant cell of the disclosure, wherein the recombinant cell treats the disease in the individual. In some embodiments, the treatment methods of the disclosure further include administering to the individual a second therapy. In some embodiments, the second therapy is selected from the group consisting of chemotherapy, radiotherapy, immunotherapy, hormonal therapy, or toxin therapy. In some embodiments, the first therapy and the second therapy are administered together, in the same composition or in separate compositions. In some embodiments, the first therapy and the second therapy are administered simultaneously. In some embodiments, the first therapy and the second therapy are administered sequentially. In some embodiments, the first therapy is administered before the second therapy. In some embodiments, the first therapy is administered after the second therapy. In some embodiments, the first therapy and the second therapy are administered in rotation.

[0029] In another aspect, provided herein are systems for modulating an activity of a cell, modulating an activity of a target cell, or treating a disease in an individual in need thereof, wherein the system includes one or more of: a chimeric polypeptide of the disclosure; a polynucleotide of the disclosure; a recombinant cell of the disclosure; or a pharmaceutical composition of the disclosure.

[0030] In another aspect, provided herein are methods for making a recombinant cell of the disclosure, including: (a) providing a cell capable of protein expression; and (b) contacting the provided cell with a recombinant nucleic acid of the disclosure. In some embodiments, the cell is obtained by leukapheresis performed on a sample obtained from a human subject or patient, and the cell is contacted *ex vivo*. In some embodiments, the recombinant nucleic acid is encapsulated in a viral capsid or a lipid nanoparticle (LNP).

[0031] In another aspect, provided herein is the use of one or more of: a chimeric polypeptide of the disclosure, a polynucleotide of the disclosure, a recombinant cell of the disclosure, or a pharmaceutical composition of the disclosure, for the treatment of a disease. In some embodiments, the disease is cancer.

[0032] In another aspect, provided herein is the use of one or more of: a chimeric polypeptide of the disclosure, a polynucleotide of the disclosure, a recombinant cell of the disclosure, or a pharmaceutical composition of the disclosure, in the manufacture of a medicament for the treatment of a disease.

[0033] The foregoing summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative embodiments and features described herein, further aspects, embodiments, objects and features of the disclosure will become fully apparent from the drawings and the detailed description and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] **FIGS. 1A-1C** schematically illustrate the experimental design and testing of exemplary non-Notch synthetic regulated intramembrane proteolysis receptors (SynRIPRs or SNIPRs) in accordance with some non-limiting embodiments of the disclosure. **FIG. 1A** schematically illustrates the modular assembly of an exemplary non-Notch SNIPR around a CLSTN2 core. **FIGS. 1B-1C** schematically summarize the results of JMD-based SNIPR tuning experiments. In these experiments, the reference receptor was an optimized CD8α Notch receptor (HingeNotch) composed of a truncated CD8α extracellular domain (ECD), a transmembrane domain (TMD) of human Notch1, and a C-terminal juxtamembrane domain (JMD) from Notch1. T cells expressing this anti-CD19 HingeNotch were able to activate a response element in the presence of CD19+ K562 sender cells. This activation was boosted when a co-expressed anti-ALPPL2 CAR is activated, providing a T cell activation stimulus. In each of these exemplary SynRIPRs, the extracellular binding domain comprises a single-chain antigen-binding fragment (scFv) having a binding affinity for a selected ligand, which in this example is the B-lymphocyte antigen CD19. As shown in **FIGS. 1B-1C**, assembly of a non-Notch SynRIPR using the CLSTN2 TMD and CLSTN2 JMD results in an inactive receptor, however the receptor function can be restored when the CLSTN2 JMD is replaced with a higher performing JMD, such as a JMD from KCNE3 or PTPRF.

[0035] **FIG. 2** depicts the experimental design of a screen for TMDs and JMDs/STSs that can be deployed in the chimeric polypeptides and non-Notch SynRIPR described herein including modular assemblies of SynRIPRs with tunable transcriptional output. In these experiments, the Notch1 JMD (STS) was kept constant for TMD selection, whereas the Notch1 TMD was kept constant for JMD (STS) selection. T cells expressing high-performing "SynRIPR → BFP expression" circuits were co-incubated with sender cells for 48 hours. BFP output was measured using flow cytometry.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0036] The present disclosure generally relates to, among other things, novel chimeric polypeptides, including a new class of synthetic receptors that do not require sequence from Notch receptors. In particular, as described in greater detail below, systematic engineering efforts have illustrated that one can utilize (1) a ADAM protease cleavable extracellular domain (*e.g.*, hinge domain from CD8), (2) a γ-secretase cleavable transmembrane domain (TMD), and (3) a stop-transfer-sequence to rationally build synthetic regulated intermembrane proteolysis receptors (SynRIPRs). As such, these receptors do not occur in nature. As described below, the chimeric polypeptides of the disclosure can be synthetic polypeptides, or can be engineered, designed, or modified so as to provide desired and/or improved properties, *e.g.*, modulating transcription.

[0037] As described in greater detail below, these receptors can be used to target various therapeutically relevant cell types to sites of disease and regulate the therapeutic activity the cell in a controlled and localized fashion. These receptors can be linked to inducible transcriptional programs such that when the cell senses a disease site it will locally produce therapeutics such as antibodies, cytokines, toxins, and adjuvants. They are a highly versatile and programmable platform for cellular engineering, and essentially the production of any genetically encodable therapeutic can regulated by these receptors. As such, the SynRIPRs described herein could be potentially be used in any of the cell therapies for cancer, autoimmunity, or the regeneration of damaged tissue. In addition, these receptors are compact in size. Polynucleotides encoding the chimeric receptors provided herein can be made smaller than existing SynNotch-encoding polynucleotides, which enables the use of vectors having more limited capacity but otherwise more desirable characteristics, or the inclusion of additional elements that would otherwise be excluded vector capacity-related size constraints. The experimental data described herein demonstrate that advanced engineering efforts can now allow scientists to rationally design receptors that function like Notch receptors but share no sequence with the Notch proteins.

[0038] In some embodiments, the present disclosure provides a new class of chimeric receptors containing a non-Notch transmembrane domain (TMD) including at least one γ-secretase site. As described in greater detail below, cleavage of the TMD is an essential step in signaling mediated by these synthetic receptors. Without being bound to any particular theory, it is believed that modulation of TMD cleavage facilitates the optimization and/or improvement of the receptors disclosed herein, which in turn can be particularly useful in modulating cell activity, *e.g.*, activating or inhibiting selected biosynthetic pathways and/or in treating diseases. In some embodiments, the receptors disclosed herein bind a target cell-surface displayed ligand, which triggers proteolytic cleavage of the receptors and release of a transcriptional regulator that modulates a custom transcriptional program in the cell.

[0039] In some embodiments, the chimeric receptors disclosed herein also include non-Notch STS sequences, which allow the new synthetic chimeric receptors of the disclosure to have a broad range of desired characteristics. For example, by altering the STS, and selecting different juxtamembrane domains, one can produce receptors having different noise levels (i.e., the basal level of receptor activation in the absence of the selected target ligand), different signal levels (i.e., the expression level obtained in the presence of the selected target ligand), and different signal:noise ratios.

[0040] Thus far, all functional SynNotch receptors have included sequence derived from Notch family members. As described in greater detail below, to demonstrate the versatility of the modular receptor assembly approach, experiments have been designed to engineer a ligand-activated receptor from the ground up based on receptor components that were completely devoid of Notch sequences. It was observed that although all receptors expressed at high levels, the otherwise-active Alcadein-gamma (CSTLN2) TMD did not function with its cognate, but inactive, STS/JMD sequence. Remarkably, it was observed that receptor signaling was restored by replacing the CSTLN2 JMD with a more active one from KCNE3 (RSRKVDKR; SEQ ID: NO: 146) or PTPRF (KRKRTH; SEQ ID: NO: 108), suggesting that the original CLSTN2 JMD is functionally limiting. The experimental results described herein illustrate the ability to build new functional synthetic regulated intramembrane proteolysis receptors from a set of functional parts, which in turns demonstrates that synthetic biology approach of receptor assembly is capable of generating receptors that function like Notch receptors but can be rationally customized in their activity.

[0041] The disclosure also provides compositions and methods useful for producing such receptors, nucleic acids encoding same, host cells genetically modified with the nucleic acids, as well as methods for modulating an activity of a cell and/or for the treatment of various diseases such as cancers.

[0042] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols generally identify similar components, unless context dictates otherwise. The illustrative alternatives described in the detailed description, drawings, and claims are not meant to be limiting. Other alternatives may be used and other changes may be made without departing from the spirit or scope of the subject matter presented here. It will be readily understood that the aspects, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, and designed in a wide variety of different configurations, all of which are explicitly contemplated and make part of this application.

Definitions

[0043] The singular form “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes one or more cells, including mixtures thereof. “A and/or B” is used herein to include all of the following alternatives: “A”, “B”, “A or B”, and “A and B.”

[0044] The terms “administration” and “administering”, as used interchangeably herein, refer to the delivery of a composition or formulation by an administration route including, but not limited to, intravenous, intra-arterial, intracerebral, intrathecal, intramuscular, intraperitoneal, subcutaneous, intramuscular, and combinations thereof. The term includes, but is not limited to, administration by a medical professional and self-administration.

[0045] The terms “host cell” and “recombinant cell” are used interchangeably herein. It is understood that such terms, as well as “cell”, “cell culture”, “cell line”, refer not only to the particular subject cell or cell line but also to the progeny or potential progeny of such a cell or cell line, without regard to the number of transfers. It should be understood that not all progeny are exactly identical to the parental cell. This is because certain modifications may occur in succeeding generations due to either mutation (*e.g.*, deliberate or inadvertent mutations) or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein, so long as the progeny retain the same functionality as that of the original cell or cell line.

[0046] As used herein, the term "construct" is intended to mean any recombinant nucleic acid molecule such as an expression cassette, plasmid, cosmid, virus, autonomously replicating polynucleotide molecule, phage, or linear or circular, single-stranded or double-stranded, DNA or RNA polynucleotide molecule, derived from any source, either capable of genomic integration or autonomous replication, including a nucleic acid molecule where one or more nucleic acid sequences has been linked in a functionally operative manner, *e.g.*, operably linked.

[0047] The term "operably linked", as used herein, denotes a physical or functional linkage between two or more elements, *e.g.*, polypeptide sequences or polynucleotide sequences, which permits them to operate in their intended fashion.

[0048] The term "heterologous", refers to nucleic acid sequences or amino acid sequences operably linked or otherwise joined to one another in a nucleic acid construct or chimeric polypeptide that are not operably linked or are not contiguous to each other in nature.

[0049] The term "percent identity," as used herein in the context of two or more nucleic acids or proteins, refers to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acids that are the same (*e.g.*, about 60% sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection. See, *e.g.*, the NCBI website at ncbi.nlm.nih.gov/BLAST. This definition also refers to, or may be applied to, the complement of a test sequence. This definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. Sequence identity can be calculated over a region that is at least about 20 amino acids or nucleotides in length, or over a region that is 10-100 amino acids or nucleotides in length, or over the entire length of a given sequence. Sequence identity can be calculated using published techniques and widely available computer programs, such as the GCS program package (Devereux et al, *Nucleic Acids Res* (1984) **12**:387), BLASTP, BLASTN, FASTA (Atschul et al., *J Mol Biol* (1990) **215**:403). Sequence identity can be measured using sequence analysis software such as the Sequence Analysis Software Package of the Genetics Computer Group at the University of Wisconsin Biotechnology Center (1710 University Avenue, Madison, Wis. 53705), with the default parameters thereof.

[0050] The term "recombinant" when used with reference to a cell, a nucleic acid, a protein, or a vector, indicates that the cell, nucleic acid, protein or vector has been altered or produced through human intervention such as, for example, has been modified by or is the result of laboratory methods. Thus, for example, recombinant cells, proteins, and nucleic acids include cells, proteins, and nucleic acids produced by laboratory methods. Recombinant proteins can include amino acid residues not found within the native (non-recombinant or wild-type) form of the protein or can be include amino acid residues that have been modified, *e.g.*, labeled. The term recombinant can include any modifications to the peptide, protein, or nucleic acid sequence. Such modifications may include the following: any chemical modifications of the peptide, protein or nucleic acid sequence, including of one or more amino acids, deoxyribonucleotides, or ribonucleotides; addition, deletion, and/or substitution of one or more of amino acids in the peptide or protein; creation of a fusion protein, *e.g.*, a fusion protein comprising an antibody fragment; and addition, deletion, and/or substitution of one or more of nucleic acids in the nucleic acid sequence. The term "recombinant" when used in reference to a cell is not intended to include naturally-occurring cells but encompass cells that have been engineered/modified to include or express a polypeptide or nucleic acid that would not be present in the cell if it was not engineered/modified.

[0051] As used herein, and unless otherwise specified, a "therapeutically effective amount" of an agent is an amount or number sufficient to provide a therapeutic benefit in the treatment or management of a health condition or disease, *e.g.*, cancer, or to delay or minimize one or more symptoms associated with the condition or disease. A therapeutically effective amount or number of a therapeutic agent means an amount or number of the therapeutic agent, alone or in combination with other therapeutic agents, which provides a therapeutic benefit in the treatment or management of the condition or disease. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition or disease, or enhances the therapeutic efficacy of another therapeutic agent. An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). The exact amount or number of a therapeutic agent including a "therapeutically effective amount" will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 2010); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (2016); Pickar, *Dosage Calculations* (2012); and *Remington: The Science and Practice of Pharmacy*, 22nd Edition, 2012, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0052] As used herein, a “subject” or an “individual” includes animals, such as human (*e.g.*, human individuals) and non-human animals. In some embodiments, a “subject” or “individual” can be a patient under the care of a physician. Thus, the subject can be a human patient or an individual who has, is at risk of having, or is suspected of having a disease of interest (*e.g.*, cancer) and/or one or more symptoms of the disease. The subject can also be an individual who is diagnosed with a risk of the condition of interest at the time of diagnosis or later. The term “non-human animals” includes all vertebrates, *e.g.*, mammals, *e.g.*, rodents, *e.g.*, mice, and non-mammals, such as non-human primates, sheep, dogs, cows, chickens, amphibians, reptiles, and the like.

[0053] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0054] Certain ranges are presented herein with numerical values being preceded by the term “about.” The term “about” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number. If the degree of approximation is not otherwise clear from the context, “about” means either within plus or minus 10% of the provided value, or rounded to the nearest significant figure, in all cases inclusive of the provided value. In some embodiments, the term “about” indicates the designated value ± up to 10%, up to ± 5%, or up to ± 1%.

[0055] It is understood that aspects and embodiments of the disclosure described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments. As used herein, “comprising” is synonymous with “including”, “containing”, or “characterized by”, and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As used herein, “consisting of” excludes any elements, steps, or ingredients not specified in the claimed composition or method. As used herein, “consisting essentially of” does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claimed composition or method. Any recitation herein of the term “comprising”, particularly in a description of components of a composition or in a description of steps of a method, is understood to encompass those compositions and methods consisting essentially of and consisting of the recited components or steps.

[0056] Headings, *e.g.,* (a), (b), (i) *etc.*, are presented merely for ease of reading the specification and claims. The use of headings in the specification or claims does not require the steps or elements be performed in alphabetical or numerical order or the order in which they are presented.

[0057] All ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, and so forth. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, and so forth. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0058] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the disclosure are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

COMPOSITIONS OF THE DISCLOSURE

[0059] As described in greater detail below, the present disclosure provides a new class of chimeric polypeptide receptors engineered to modulate transcriptional regulation in a ligand-dependent manner having multiple advantages over existing synthetic receptors. In particular, some embodiments of the disclosure provides synthetic receptors that do not require sequence from Notch receptors. In some embodiments, inclusion of a heterologous TMD provides the new synthetic receptors with a variety of improved expression characteristics, thus expanding the palette of available receptors available to the cellular engineer. In some embodiments, the synthetic receptors disclosed herein also include non-Notch STS sequences, which allow the new synthetic receptors to have a broad range of desired characteristics. In addition, as discussed above, these new synthetic receptors are compact in size, such that polynucleotides encoding these synthetic receptors can be made smaller than existing SynNotch-encoding polynucleotides, which enables the use of vectors having more limited capacity but otherwise more desirable characteristics, or the inclusion of additional elements that would otherwise be excluded vector capacity-related size constraints.

[0060] As illustrated below, the ability to build new functional synthetic regulated intramembrane proteolysis receptors from a set of functional parts shows that synthetic biology approaches of receptor assembly are capable of generating receptors that function like naturally occurring receptors, such as Notch receptors, but can be rationally to customize their activity.

[0061] One skilled in the art will understand that the chimeric polypeptide receptors disclosed herein facilitate amplified activation under certain specific cellular and environmental contexts. This type of feedback on the receptor activity is a new feature that can be exploited to enhance and tune the expression of therapeutic payloads by engineered cells. As described in the Examples herein, chimeric polypeptide receptors have been tested and validated in primary human T cells. Without being bound to any particular theory, it is contemplated that these new receptors show similar performance in other mammalian cells. In addition, one of ordinary skill in the art, upon reviewing the present disclosure, will appreciate that the synthetic receptors disclosed herein may be engineered into various immune cell types for enhanced discrimination and elimination of tumors, or in engineered cells for tunable control of autoimmunity and tissue regeneration. Accordingly, engineered cells, such as immune cells engineered to express one of more of the chimeric receptors disclosed herein, are also within the scope of the disclosure.

Chimeric Polypeptides

[0062] In one aspect, provided herein are a variety of novel, non-naturally occurring chimeric polypeptides engineered to modulate transcriptional regulation in a ligand-dependent manner. These new receptors generally include (1) a γ-secretase cleavable transmembrane domain (TMD), and (2) a stop-transfer-sequence. Inclusion of heterologous STS and TMD sequences facilitates the optimization and/or improvement of the new chimeric receptors disclosed herein, which in turn is useful in modulating cell activity and/or in treating diseases. In some embodiments, the receptors provided herein bind a target cell-surface displayed ligand, triggering proteolytic cleavage of the receptors and releasing a transcriptional regulator that modulates a custom transcriptional program in the cell.

[0063] In some embodiments, provided herein is a chimeric polypeptide including, from N-terminus to C-terminus: (a) an extracellular binding domain having a binding affinity for a selected ligand; (b) a linking sequence; (c) a TMD having at least about 80% sequence identity to the transmembrane domain of a Type 1 transmembrane receptor and including one or more ligand-inducible proteolytic cleavage sites; and (d) an ICD including a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site between the transcriptional regulator and the linking sequence, and wherein the chimeric polypeptide does not include a sequence from a Notch receptor.

Extracellular domain (ECD)

[0064] In some embodiments, the ECD of the chimeric polypeptides and chimeric receptors (*e.g.*, SynRIPRs) disclosed herein has a binding affinity for one or more target ligands. In principle, there are no particular limitations with regard to suitable ligands that may be targeted by the chimeric polypeptides provided herein. In some embodiments, the target ligand is a cell-surface ligand. Non-limiting examples of suitable cell-surface ligands include cell surface receptors; adhesion proteins; carbohydrates, lipids, glycolipids, lipoproteins, and lipopolysaccharides that are surface-bound; integrins; mucins; and lectins. In some embodiments, the ligand is a protein. In some embodiments, the ligand is a carbohydrate.

[0065] In some embodiments, the extracellular domain includes the ligand-binding portion of a receptor. In some embodiments, the extracellular domain includes an antigen-binding moiety that binds to one or more target antigens. In some embodiments, the ECD includes an antigen-binding moiety capable of binding to one or more antigens on the surface of a cell (*e.g.*, cell surface antigens). In some embodiments, the antigen-binding moiety includes one or more antigen-binding determinants of an antibody or a functional antigen-binding fragment thereof. One skilled in the art upon reading the present disclosure will readily understand that the term "functional fragment thereof" or "functional variant thereof" refers to a molecule having biological activity in common with the wild-type molecule from which the fragment or variant was derived. For example, a functional fragment or a functional variant of an antibody is one which retains essentially the same ability to bind to the same epitope as the antibody from which the functional fragment or functional variant was derived. For example, an antibody capable of binding to an epitope of a cell surface receptor may be truncated at the N-terminus and/or C-terminus, and the retention of its epitope binding activity assessed using assays known to those of skill in the art. In some embodiments, the antigen-binding moiety is selected from the group consisting of an antibody, a nanobody, a diabody, a triabody, or a minibody, a $F(ab')_2$ fragment, a Fab fragment, a single chain variable fragment (scFv), and a single domain antibody (sdAb), or a functional fragment thereof. In some embodiments, the antigen-binding moiety includes an scFv.

[0066] The antigen-binding moiety can include naturally-occurring amino acid sequences or can be engineered, designed, or modified so as to provide desired and/or improved properties, *e.g.*, binding affinity. Generally, the binding affinity of an antigen-binding moiety, *e.g.*, an antibody, for a target antigen (*e.g.*, CD19 antigen) can be calculated by the Scatchard method described by Frankel et al., *Mol Immunol* (1979) **16**:101-06. In some embodiments, binding affinity is measured by an antigen/antibody dissociation rate. In some embodiments, binding affinity is measured by a competition radioimmunoassay. In some embodiments, binding affinity is measured by ELISA. In some embodiments, antibody affinity is measured by flow cytometry. An antibody that "selectively binds" an antigen (such as CD19) is an antigen-binding moiety that binds the antigen with high affinity and does not significantly bind other unrelated antigens.

[0067] A skilled artisan can select an extracellular domain based on the desired localization or function of a cell that is genetically modified to express a chimeric polypeptide or SynRIPR of the present disclosure. For example, the extracellular domain can be selected to target a receptor-expressing cell to estrogen-dependent breast cancer cells. In some embodiments, the extracellular domain of the disclosed chimeric polypeptide receptors (*e.g.*, SynRIPRs) is capable of binding a tumor-associated antigen (TAA) or a tumor-specific antigen (TSA). TAAs include a molecule, such as, for example, a protein, present on tumor cells and on a sub-population of normal cells, or on many normal cells, but at much lower concentration than on tumor cells. Examples include, without limitation, CEA, AFP, HER2, CTAG1B and MAGEA1. In contrast, TSAs generally include a molecule, such as, *e.g.*, a protein, present on tumor cells but not expressed on normal cells. Examples include, without limitation, oncoviral antigens and mutated proteins (also known as neoantigens).

[0068] In some cases, the antigen-binding moiety is specific for an epitope present in an antigen that is expressed by a tumor cell, i.e., a tumor-associated antigen or a tumor-specific antigen. The tumor-associated or tumor-specific antigen can be an antigen associated with, *e.g.*, a breast cancer cell, a B cell lymphoma, a pancreatic cancer, a Hodgkin lymphoma cell, an ovarian cancer cell, a prostate cancer cell, a mesothelioma, a lung cancer cell, a non-Hodgkin B-cell lymphoma (B-NHL) cell, an ovarian cancer cell, a prostate cancer cell, a mesothelioma cell, a melanoma cell, a chronic lymphocytic leukemia cell, an acute lymphocytic leukemia cell, a neuroblastoma cell, a glioma, a glioblastoma, a colorectal cancer cell, and the like. It will also be understood that a tumor-associated antigen may also be expressed by a non-cancerous cell. In some embodiments, the antigen-binding domain is specific for an epitope present in a tissue-specific antigen. In some embodiments, the antigen-binding domain is specific for an epitope present in a disease-associated antigen.

[0069] Generally, there are no particular limitations with regard to suitable surface antigens that may be targeted by the chimeric polypeptide receptors disclosed herein. Non-limiting examples of suitable target antigens include CD19, B7H3 (CD276), BCMA (CD269), alkaline phosphatase, placental-like 2 (ALPPL2), green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), signal regulatory protein α (SIRPα), CD123, CD171, CD179a, CD20, CD213A2, CD22, CD24, CD246, CD272, CD30, CD33, CD38, CD44v6, CD46, CD71, CD97, CEA, CLDN6, CLECL1, CS-1, EGFR, EGFRvIII, ELF2M, EpCAM, EphA2, Ephrin B2, FAP, FLT3, GD2, GD3, GM3, GPRC5D, HER2 (ERBB2/neu), IGLL1, IL-11Ra, KIT (CD117), MUC1, NCAM, PAP, PDGFR-β, PRSS21, PSCA, PSMA, ROR1, SSEA-4, TAG72, TEM1/CD248, TEM7R, TSHR, VEGFR2, ALPI, citrullinated vimentin, cMet, and Axl.

[0070] In some embodiments, the target antigen is selected from CD19, B7H3 (CD276), BCMA (CD269), CD123, CD171, CD179a, CD20, CD213A2, CD22, CD24, CD246, CD272, CD30, CD33, CD38, CD44v6, CD46, CD71, CD97, CEA, CLDN6, CLECL1, CS-1, EGFR, EGFRvIII, ELF2M, EpCAM, EphA2, Ephrin B2, FAP, FLT3, GD2, GD3, GM3, GPRC5D, HER2 (ERBB2/neu), IGLL1, IL-11Ra, KIT (CD117), MUC1, NCAM, PAP, PDGFR-β, PRSS21, PSCA, PSMA, ROR1, SSEA-4, TAG72, TEM1/CD248, TEM7R, TSHR, VEGFR2, ALPI, citrullinated vimentin, cMet, Axl, GPC2, human epidermal growth factor receptor 2 (Her2/neu), CD276 (B7-H3), IL-13Rα1, IL-13Rα2, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD123, CD93, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), ALK, DLK1, FAP, NY-ESO, WT1, HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, AOC3 (VAP-1), CAM-3001, CCL11 (eotaxin-1), CD125, CD147 (basigin), CD154 (CD40L), CD2, CD20, CD23 (IgE receptor), CD25 (a chain of IL-2 receptor), CD3, CD4, CD5, IFN-α, IFN-γ, IgE, IgE Fc region, IL-1, IL-12, IL-23, IL-13, IL-17, IL-17A, IL-22, IL-4, IL-5, IL-5, IL-6, IL-6 receptor, integrin α4, integrin α4β7, LFA-1 (CD11α), myostatin, OX-40, scleroscin, SOST, TGFβ1, TNF-α, VEGF-A, pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD20, CD5, CD7, CD3, TRBC1, TRBC2, CD38, CD123, CD93, CD34, CD1a, SLAMF7/CS1, FLT3, CD33, CD123, TALLA-1, CSPG4, DLL3, Kappa light chain, Lamba light chain, CD16/ FcγRIII, CD64, FITC, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), GD3, EGFRvIII (epidermal growth factor variant III), EGFR and isovariants thereof, TEM-8, sperm protein 17 (Sp17), and mesothelin.

[0071] Further non-limiting examples of suitable antigens include PAP (prostatic acid phosphatase), prostate stem cell antigen (PSCA), prostein, NKG2D, TARP (T cell receptor γ alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, an abnormal p53 protein, integrin β3 (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), Ral-B, GPC2, CD276 (B7-H3), or IL-13Rα. In some embodiments, the antigen is ALPPL2. In some embodiments, the antigen is BCMA. In some embodiments, the antigen-binding moiety of the ECD is specific for a reporter protein, such as GFP and eGFP. Non-limiting examples of such antigen binding moiety include a LaG17 anti-GFP nanobody. In some embodiments, the antigen-binding moiety of the ECD includes an anti-BCMA fully-humanized VH domain (FHVH). In some embodiments, the antigen is signal regulatory protein α (SIRPα).

[0072] Additional antigens that can be suitable for the chimeric polypeptide receptors disclosed herein include, but are not limited to GPC2, human epidermal growth factor receptor 2 (Her2/neu), CD276 (B7-H3), IL-13Rα1, IL-13Rα2, α-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA). Other suitable target antigens include, but are not limited to, tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD123, CD93, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), ALK, DLK1, FAP, NY-ESO, WT1, HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1.

[0073] Additional suitable antigens include, but are not limited to, those associated with an inflammatory disease such as, AOC3 (VAP-1), CAM-3001, CCL11 (eotaxin-1), CD125, CD147 (basigin), CD154 (CD40L), CD2, CD20, CD23 (IgE receptor), CD25 (one subunit of the heterodimeric IL-2 receptor), CD3, CD4, CD5, IFNα, IFNγ, IgE, IgE Fc region, IL-1, IL-12, IL-23, IL-13, IL-17, IL-17A, IL-22, IL-4, IL-5, IL-5, IL-6, IL-6 receptor, integrin α4, integrin α4β7, LFA-1 (CD11α), myostatin, OX-40, scleroscin, SOST, TGFβ1, TNFα, and VEGF-A.

[0074] Further antigens suitable for the chimeric polypeptides and SynRIPRs disclosed herein include, but are not limited to the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD20, CD5, CD7, CD3, TRBC1, TRBC2, BCMA, CD38, CD123, CD93, CD34, CD1a, SLAMF7/CS1,

FLT3, CD33, CD123, TALLA-1, CSPG4, DLL3, Kappa light chain, Lamba light chain, CD16/ FcγRIII, CD64, FITC, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), GD3, EGFRvIII (epidermal growth factor variant III), EGFR and isovariants thereof, TEM-8, sperm protein 17 (Sp17), mesothelin. Further non-limiting examples of suitable antigens include PAP (prostatic acid phosphatase), prostate stem cell antigen (PSCA), prostein, NKG2D, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate-1), an abnormal ras protein, an abnormal p53 protein, integrin β3 (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), and Ral-B. In some embodiments, the antigen is ALPPL2. In some embodiments, the antigen is BCMA. In some embodiments, the antigen-binding moiety of the ECD is specific for a reporter protein, such as GFP and eGFP. Non-limiting examples of such antigen binding moiety include a LaG17 anti-GFP nanobody. In some embodiments, the antigen-binding moiety of the ECD includes an anti-BCMA fully-humanized VH domain (FHVH). In some embodiments, the antigen is signal regulatory protein α (SIRPα).

[0075] In some embodiments, antigens suitable for targeting by the chimeric polypeptides and chimeric receptors disclosed herein include ligands derived from a pathogen. For example, the antigen can be HER2 produced by HER2-positive breast cancer cells. In some embodiments, the antigen can be CD19 that is expressed on B-cell leukemia. In some embodiments, the antigen can be EGFR that is expressed on glioblastoma multiform (GBM) but much less expressed so on healthy CNS tissue. In some embodiments, the antigen can be CEA that is associated with cancer in adults, for example colon cancer.

[0076] In some embodiments, the antigen-binding moiety of the extracellular domain is specific for a cell surface target, where non-limiting examples of cell surface targets include CD19, CD30, Her2, CD22, ENPP3, EGFR, CD20, CD52, CD11α, and α-integrin. In some embodiments, the chimeric polypeptides and SynRIPRs disclosed herein include an extracellular domain having an antigen-binding moiety that binds CD19, CEA, HER2, MUC1, CD20, or EGFR. In some embodiments, the chimeric polypeptides and SynRIPRs disclosed herein include an extracellular domain including an antigen-binding moiety that binds CD19.

Linking Sequence

[0077] As described above, the chimeric polypeptides and receptors of the disclosure include a linking sequence disposed between the extracellular ligand-binding domain (ECD) and the TMD.

[0078] In some embodiments, the linking sequence of the chimeric receptors has at least about 80% amino acid sequence identity to a polypeptide hinge domain. Without being bound to any particular theory, the hinge domain of the chimeric polypeptides and SynRIPRs disclosed herein may serve several functions, including controlling flexibility and rigidity of the chimeric polypeptides and SynRIPRs, which in turn can affect antigen binding and signal transduction. The length of the hinge domain can be tuned to enhance the SynRIPRs' ability to reach antigens in the space between a SynRIPR and a target cell. The hinge domain can also be tuned to mediate dimerization. Care should be taken in selecting a suitable hinge domain. For example, shorter hinge domain may be more rigid and more effective at transducing signal once engaged on target antigen but may not reach target that are more membrane proximal or otherwise specially constrained. In some embodiments, the hinge domain is capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding. In these instances, within the chimeric polypeptides and SynRIPRs disclosed herein, the hinge domain generally includes a flexible oligo- or polypeptide connector region disposed between the ECD and the TMD. Thus, the hinge domain provides flexibility between the ECD and TMD and also provides sites for intermolecular disulfide bonding between two or more chimeric polypeptide monomers to form an oligomeric complex. In some embodiments, the hinge domain includes motifs that promote dimer formation of the chimeric polypeptides disclosed herein. In some embodiments, the hinge domain includes motifs that promote trimer formation of the chimeric polypeptides disclosed herein (*e.g.*, a hinge domain derived from OX40).

[0079] Hinge polypeptide sequences suitable for the compositions and methods of the disclosure can be naturally-occurring hinge polypeptide sequences (*e.g.*, those from naturally-occurring immunoglobulins). Alternatively, a hinge polypeptide sequence can be a synthetic sequence that corresponds to a naturally-occurring hinge polypeptide sequence, or can be an entirely synthetic hinge sequence, or can be engineered, designed, or modified to provide desired and/or improved properties, *e.g.*, modulating transcription. Suitable hinge polypeptide sequences include, but are not limited to, those derived from IgA, IgD, and IgG subclasses, such as IgG1 hinge domain, IgG2 hinge domain, IgG3 hinge domain, and IgG4 hinge domain, or a functional variant thereof. In some embodiments, the hinge polypeptide sequence contains one or more CXXC motifs. In some embodiments, the hinge polypeptide sequence contains one or more CPPC motifs. Additional information in this regard can be found in, for example, a recent review by Vidarsson G. *et al.*, *Frontiers Immunol.* October 20, 2014, which is hereby incorporated by reference in its entirety.

[0080] Accordingly, in some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgG1 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgG2 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgG3 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgG4 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgA hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgD hinge domain or a functional variant thereof.

[0081] Additional hinge polypeptide sequences suitable for the compositions and methods disclosed herein include, but are not limited to, hinge polypeptide sequences derived from a CD8α hinge domain, a CD28 hinge domain, a CD152 hinge domain, a PD-1 hinge domain, a CTLA4 hinge domain, an OX40 hinge domain, an FcγRIIIα hinge domain, and functional variants thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from a CD8α hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from a CD28 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an OX40 hinge domain or a functional variant thereof. In some embodiments, the hinge domain includes a hinge polypeptide sequence derived from an IgG4 hinge domain or a functional variant thereof.

[0082] In principle, there are no particular limitations to the length and/or amino acid composition of the hinge domain other than it confers flexibility and the capacity for oligomerization. However, one skilled in the art will readily appreciate that the length and amino acid composition of the hinge polypeptide sequence can be optimized to vary the orientation and/or proximity of the ECD and the TMD relative to one another, as well as of the chimeric polypeptide monomers to one another, to achieve a desired activity of the chimeric polypeptide of the disclosure. In some embodiments, any single-chain peptide including about one to 100 amino acid residues (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, *etc.*

amino acid residues) can be used as a hinge domain. In some embodiments, the hinge domain includes about 5 to 50, about 10 to 60, about 20 to 70, about 30 to 80, about 40 to 90, about 50 to 100, about 60 to 80, about 70 to 100, about 30 to 60, about 20 to 80, about 30 to 90 amino acid residues. In some embodiments, the hinge domain includes about 1 to 10, about 5 to 15, about 10 to 20, about 15 to 25, about 20 to 40, about 30 to 50, about 40 to 60, about 50 to 70 amino acid residues. In some embodiments, the hinge domain includes about 40 to 70, about 50 to 80, about 60 to 80, about 70 to 90, or about 80 to 100 amino acid residues. In some embodiments, the hinge domain includes about 1 to 10, about 5 to 15, about 10 to 20, about 15 to 25 amino acid residues.

[0083] In some embodiments, the linking sequence comprises an amino acid sequence having at least 80% sequence identity to a hinge domain derived from CD8α hinge domain, a CD28 hinge domain, a CD152 hinge domain, a PD-1 hinge domain, a CTLA4 hinge domain, an OX40 hinge domain, an IgG1 hinge domain, an IgG2 hinge domain, an IgG3 hinge domain, and an IgG4 hinge domain, or a functional variant of any thereof.

[0084] In some embodiments, the hinge domain is derived from a CD8α hinge domain or a functional variant thereof. In some embodiments, the hinge domain comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 157-161.

[0085] In some embodiments, the linking sequence comprises or consists of an amino acid sequence having at least about 80% sequence identity, such as, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or about 99% sequence identity to a sequence set forth in SEQ ID NOS: 157-161 in the Sequence Listing. In some embodiments, the linking sequence comprises or consists of an amino acid sequence having at least about 80% sequence identity to a sequence set forth in SEQ ID NOS: 157-161. In some embodiments, the linking sequence comprises or consists of an amino acid sequence having at least about 90% sequence identity to a sequence set forth in SEQ ID NOS: 157-161. In some embodiments, the linking sequence comprises or consists of an amino acid sequence having at least about 95% sequence identity to a sequence set forth in SEQ ID NOS: 157-161. In some embodiments, the linking sequence comprises or consists of an amino acid sequence having about 100% sequence identity to a sequence set forth in SEQ ID NOS: 157-161. In some embodiments, the linking sequence comprises or consists of an amino acid sequence selected from the group consisting of

SEQ ID NOS: 157-161, wherein one, two, three, four, or five of the amino acid residues in any one of SEQ ID NO: 157-161 is/are substituted by a different amino acid residues.

[0086] In some embodiments, one or more domains of a ROBO (Roundabout) cell surface receptor are incorporated into the linking sequence of the chimeric receptors of the present disclosure. ROBO receptors release a nuclear transcription factor domain following ligand-induced cleavage of the extracellular portion of the receptor by the ADAM10 MMP and γ-secretase. However, ROBO does not contain a LIN/Notch domain, EGF-like repeats, or an HD domain. Additionally, the primary ligand for ROBO is a soluble protein (SLIT). Mammals have four ROBO receptors: ROBO1-3 have five immunoglobulin-like (Ig) domains, three fibronectin (Fn) repeats, and a transmembrane domain linked to an intracellular domain. ROBO4 has only two Ig domains, and two Fn domains. Additional information in this regard can be found in, for example, H. Blockus et al., *Development* (2016) **143**:3037-44, which is hereby incorporated by reference.

[0087] In some embodiments, the linking sequence of the chimeric receptors as disclosed herein includes at least one fibronectin (Fn) repeat derived from a ROBO receptor. The linking sequence of the disclosed chimeric receptors can contain 1, 2, 3, 4, or 5 Fn repeats. In some embodiments, the l linking sequence of the chimeric receptors includes about 1 to about 5 Fn repeats, about 1 to about 3 Fn repeats, or about 2 to about 3 Fn repeats. In some embodiments, the linking sequence of the chimeric receptors has at least about 80% amino acid sequence identity to a ROBO1 JMD including at least one fibronectin repeat.

[0088] In some embodiments, the linking sequence of the chimeric receptors has a polypeptide sequence of about 4 to about 40 amino acid residues in length (*e.g.*, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acid residues). In some embodiments, the length and amino acid composition of the linking sequence can be optimized to vary the orientation and/or proximity of the ECD and the TMD relative to one another to achieve a desired activity of the chimeric polypeptide of the disclosure. In some embodiments, the linking sequence of the chimeric receptors has a polypeptide sequence of about 4 to about 40, about 5 to about 30, about 10 to about 20, about 10 to about 30, about 10 to about 40, about 5 to about 20, about 5 to about 40, or about 20 to about 40 amino acid residues in length.

Transmembrane domain (TMD)

[0089] As described above, the chimeric receptors of the disclosure include a transmembrane domain having at least about 80% sequence identity to the TMD of a Type 1 transmembrane receptor and comprising one or more ligand-inducible proteolytic cleavage sites.

[0090] Examples of proteolytic cleavage sites suitable for the compositions and methods disclosed herein include, but are not limited to, a metalloproteinase cleavage site for a matrix metalloproteinase (MMP) selected from collagenase-1, -2, and -3 (MMP-1, - 8, and -13), gelatinase A and B (MMP-2 and -9), stromelysin 1, 2, and 3 (MMP-3, -10, and -11), matrilysin (MMP-7), and membrane metalloproteinases (MT1-MMP and MT2-MMP). For example, the cleavage sequence of MMP-9 is Pro-X-X-Hy (wherein, X represents an arbitrary residue; Hy, a hydrophobic residue such as Leu, Ile, Val, Phe, Trp, Tyr, Val, Met, and Pro) (SEQ ID NO: 165), *e.g.*, Pro-X-X-Hy-(Ser/Thr) (SEQ ID NO: 166), *e.g.*, Pro-Leu/Gln-Gly-Met-Thr-Ser (SEQ ID NO: 167) or Pro-Leu/Gln-Gly-Met-Thr (SEQ ID NO: 168. Another example of a suitable protease cleavage site is a plasminogen activator cleavage site, *e.g.*, a urokinase plasminogen activator (uPA) or a tissue plasminogen activator (tPA) cleavage site. Another example of a suitable protease cleavage site is a prolactin cleavage site. Specific examples of cleavage sequences of uPA and tPA include sequences comprising Val-Gly-Arg (SEQ ID NO: 169). Another example of a protease cleavage site that can be included in a proteolytically cleavable linker is a tobacco etch virus (TEV) protease cleavage site, *e.g.*, Glu-Asn-Leu-Tyr-Thr-Gln-Ser (SEQ ID NO: 170), where the protease cleaves between the glutamine and the serine. Another example of a protease cleavage site that can be included in a proteolytically cleavable linker is an enterokinase cleavage site, *e.g.*, Asp-Asp-Asp-Asp-Lys (SEQ ID NO: 171), where cleavage occurs after the lysine residue. Another example of a protease cleavage site that can be included in a proteolytically cleavable linker is a thrombin cleavage site, *e.g.*, Leu-Val-Pro-Arg (SEQ ID NO: 172). Additional suitable linkers comprising protease cleavage sites include sequences cleavable by the following proteases: a PreScission™ protease (a fusion protein comprising human rhinovirus 3C protease and glutathione-S-transferase), a thrombin, cathepsin B, Epstein-Barr virus protease, MMP-3 (stromelysin), MMP-7 (matrilysin), MMP-9; thermolysin-like MMP, matrix metalloproteinase 2 (MMP-2), cathepsin L; cathepsin D, matrix metalloproteinase l (MMP-l), urokinase-type plasminogen activator, membrane type 1 matrix metalloproteinase (MT-MMP), stromelysin 3 (or MMP-11), thermolysin, fibroblast collagenase and stromelysin-1, matrix metalloproteinase 13 (collagenase-3), tissue-type plasminogen activator (tPA), human prostate-specific antigen, kallikrein (hK3), neutrophil elastase, and calpain (calcium activated neutral protease). Proteases that are not native to the host cell in which the receptor is expressed (for example, TEV) can be used as a further regulatory mechanism, in which activation of the SynRIPR of the disclosure is reduced until the protease is expressed or otherwise provided. Additionally, a protease may be tumor-associated or disease-associated (expressed to a significantly higher degree than in normal tissue), and serve as an independent regulatory mechanism. For example, some matrix metalloproteases are highly expressed in certain cancer types.

[0091] Generally, the TMD suitable for the chimeric receptors disclosed herein can be any transmembrane domain of a Type 1 transmembrane receptor comprising at least one γ-secretase cleavage site. Detailed description of the structure and function of the γ-secretase complex as well as its substrate proteins, including amyloid precursor protein (APP), can, for example, be found in a recent review by Zhang et al., *Frontiers Cell Neurosci* (2014). Non-limiting suitable TMDs from Type 1 transmembrane receptors include those from CLSTN1, CLSTN2, APLP1, APLP2, LRP8, APP, BTC, TGBR3, SPN, CD44, CSF1R, CXCL16, CX3CL1, DCC, DLL1, DSG2, DAG1, CDH1, EPCAM, EPHA4, EPHB2, EFNB1, EFNB2, ErbB4, GHR, HLA-A, and IFNAR2, wherein the TMD includes at least one γ-secretase cleavage site. Additional TMDs suitable for the compositions and methods described herein include, but are not limited to, transmembrane domains from Type 1 transmembrane receptors IL1R1, IL1R2, IL6R, INSR, ERN1, ERN2, JAG2, KCNE1, KCNE2, KCNE3, KCNE4, KL, CHL1, PTPRF, SCN1B, SCN3B, NPR3, NGFR, PLXDC2, PAM, AGER, ROBO1, SORCS3, SORCS1, SORL1, SORT1, SDC1, SDC2, SPN, TYR, TYRP1, DCT, VASN, FLT1, CDH5, PKHD1, NECTIN1, PCDHGC3, NRG1, LRP1B, CDH2, NRG2, PTPRK, SCN2B, Nradd, and PTPRM. In some embodiments, the TMD of the chimeric polypeptides or SynRIPRs of the disclosure is a TMD derived from the TMD of APP, CLSTN1, CLSTN2, EPCAM, KCNE3, NECTIN1, PCDHGC3, and PTPRF. In some embodiments, the TMD of the chimeric polypeptides or SynRIPRs of the disclosure is a TMD derived from the TMD of a member of the calsyntenin family, such as, alcadein alpha and alcadein gamma.

[0092] Accordingly, in some embodiments, the transmembrane domain includes an amino acid sequence exhibiting at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% sequence identity to a polypeptide sequence having at least about 70% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor that comprises a γ-secretase cleavage site. In some embodiments, the transmembrane domain includes an amino acid sequence exhibiting at least 70% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor that comprises a γ-secretase cleavage site. In some embodiments, the transmembrane domain includes an amino acid sequence exhibiting at least about 80% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor that comprises a γ-secretase cleavage site. In some embodiments, the transmembrane domain includes an amino acid sequence exhibiting at least about 90% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor that comprises a γ-secretase cleavage site. In some embodiments, the transmembrane domain includes an amino acid sequence exhibiting at least about 95% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor that comprises a γ-secretase cleavage site. In some embodiments, the Type 1 transmembrane receptor is selected from the group consisting of CLSTN1, CLSTN2, APLP1, APLP2, LRP8, APP, BTC, TGBR3, SPN, CD44, CSF1R, CXCL16, CX3CL1, DCC, DLL1, DSG2, DAG1, CDH1, EPCAM, EPHA4, EPHB2, EFNB1, EFNB2, ErbB4, GHR, HLA-A, IFNAR2, IL1R1, IL1R2, IL6R, INSR, ERN1, ERN2, JAG2, KCNE1, KCNE2, KCNE3, KCNE4, KL, CHL1, PTPRF, SCN1B, SCN3B, NPR3, NGFR, PLXDC2, PAM, AGER, ROBO1, SORCS3, SORCS1, SORL1, SORT1, SDC1, SDC2, TYR, TYRP1, DCT, VASN, FLT1, CDH5, PKHD1, NECTIN1, PCDHGC3, NRG1, LRP1B, CDH2, NRG2, PTPRK, SCN2B, Nradd, and PTPRM. In some embodiments, the TMD includes an amino acid sequence exhibiting at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192 in the Sequence Listing. In some embodiments, the transmembrane domain includes an amino acid sequence having at least about 90% sequence identity to SEQ ID NOS: 1-84, 178, 182-185, and 190-192. In some embodiments, the transmembrane domain includes an amino acid sequence having at least about 95% sequence identity to SEQ ID NOS: 1-88. In some embodiments, the transmembrane domain includes an amino acid sequence having about 100% sequence identity to SEQ ID NOS: 1-84, 178, 182-185, and 190-192. In some embodiments, the transmembrane domain includes the amino acid sequence of SEQ ID NO: 1-

84, 178, 182-185, and 190-192, wherein one, two, three, four, or five of the amino acid residues in the amino acid sequence is/are substituted by a different amino acid residue.

[0093] In some embodiments, the amino acid substitution(s) within the TMD includes one or more substitutions within a "GV" motif of the TMD. In some embodiments, at least one of such substitution(s) comprises a substitution to alanine. For example, one, two, three, four, five, or more of the amino acid residues of the sequence IATVVIIISVCMLVFVVAMGVY (SEQ ID NO: 2), as well as any one of sequences as set forth in SEQ ID NOS: 1, 6, 20, 43, 39, 54, and 64, may be substituted by a different amino acid residue. In some embodiments, the amino acid residue at position 18 and/or 19 of the "GV" motif within SEQ ID NO: 2 is substituted by a different amino acid residue. In some embodiments, the glycine residue at position 20 of SEQ ID NO: 2 is substituted by a different amino acid residue. In some embodiments, the valine residue at position 21 of SEQ ID NO: 2 is substituted by a different amino acid residue. In some embodiments, the transmembrane domain comprises an amino acid sequence having a sequence corresponding to SEQ ID NO: 2 with a mutation at the position corresponding to position 18 of SEQ ID NO: 20, such as G18A mutations. In some embodiments, the transmembrane domain comprises an amino acid sequence having a sequence corresponding to SEQ ID NO: 2 with a mutation at the position corresponding to position 21 of SEQ ID NO: 57, such as V19A mutations.

Stop-transfer sequence (STS)

[0094] In some embodiments, the chimeric receptors of the disclosure include a stop-transfer sequence (STS), which is essentially a highly-charged domain located between the TMD and the ICD. Without being bound to any particular theory, such a highly-charged domain disposed between the TMD and the ICD prevents the ICD from entering the membrane. In principle, there are no particular limitations to the length and/or amino acid composition of the STS. In some embodiments, any arbitrary single-chain peptide comprising about 1 to about 40 amino acid residues (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acid residues) can be used as an STS. In some embodiments, the STS includes about 1 to 15, about 5 to 20, about 8 to 25, about 10 to 30, about 12 to 35, about 14 to 40, about 5 to 40, about 10 to 35, about 15 to 30, about 20 to 25, about 20 to 40, about 10 to 30, about 4 to 20, or about 5 to 25 amino acid residues. In some embodiments, the STS includes about 1 to 10, about 5 to 12, about 6 to 14, about 7 to 18, about 8 to 20, about 9 to 22, about 10 to 24, or about 11 to 26 amino acid residues. In some embodiments, the STS includes about 4 to 10 residues, such as, 4, 5, 6, 7, 8, 9, or 10 amino acid residues.

[0095] In some embodiments, the STS includes a sequence having at least about 80% sequence identity, such as, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 99% sequence identity to the STS domain of a Type 1 receptor. In some embodiments, the STS includes an amino acid sequence having at least 90% sequence identity to the STS domain of a Type 1 receptor. In some embodiments, the STS includes a sequence having at least 70% sequence identity, such as, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 99% sequence identity to a STS sequence from CSF1R, CXCL16, DAG1, GHR, PTPRF, AGER, KL, NRG1, LRP1B, Jag2, EPCAM, KCNE3, CDH2, NRG2, PTPRK, BTC, EPHA3, IL1R2, PTPRF, or PTPRM. In some embodiments, the STS includes a sequence having at least 70% sequence identity, such as, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 99% sequence identity to a STS sequence from CSF1R, DAG1, AGER, NRG1, KCNE3, PTPRF, or PTPRM. In some embodiments, the STS includes a sequence comprising only Lys (K) or Arg (R) in the first 4 residues. In some embodiments, the STS includes one, two, three, four, five, or more basic residues. In some embodiments, the STS includes five, four, three, two, one, or zero aromatic residues or residues with hydrophobic and/or bulky side chains.

[0096] In some embodiments, the STS includes a sequence having at least 80% sequence identity, such as, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or 99% sequence identity to SEQ ID NO: 85-156 and 173 in the Sequence Listing. In some embodiments, the STS includes an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the STS includes an amino acid sequence having at least 95% sequence identity to SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the STS includes an amino acid sequence having at least 100% sequence identity to SEQ ID NO: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the STS includes an amino acid sequence having at least 90% or at least 95% sequence identity to SEQ ID NO: 146. In some embodiments, the STS includes an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 108. In some embodiments, the STS includes the amino acid sequence of any one of SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156, wherein one, two, three, four, or five of the amino acid residues in the amino acid sequence is/are substituted by a different amino acid residue.

Intracellular domain (ICD)

[0097] The chimeric receptor of the disclosure further comprises an intracellular domain (ICD) comprising a transcriptional regulator. The transcriptional regulator is a biochemical element that acts to activate or repress the transcription of a promoter-driven DNA sequence. Transcriptional regulators suitable for the compositions and methods of the disclosure can be naturally-occurring transcriptional regulators or can be engineered, designed, or modified so as to provide desired and/or improved properties, *e.g.*, modulating transcription. In some embodiments, the transcriptional regulator directly regulates expression of one or more genes involved in differentiation of the cell. In some embodiments, the transcriptional regulator indirectly modulates expression of one or more genes involved in differentiation of the cell by modulating the expression of a second transcription factor which in turn modulates expression of one or more genes involved in differentiation of the cell. It will be understood by a skilled artisan that a transcriptional regulator can be a transcriptional activator or a transcriptional repressor. In some embodiments, the transcriptional regulator is a transcriptional repressor. In some embodiments, the transcriptional regulator is a transcriptional activator. In some embodiments, the transcriptional regulator can further include a nuclear localization signal. In some embodiments, the transcriptional regulator is selected from Gal4-VP16, Gal4-VP64, tetR-VP64, ZFHD1-VP64, Gal4-KRAB, and HAP1-VP16. In some embodiments, the transcriptional regulator is Gal4-VP64.

Additional domains

[0098] In some embodiments, the extracellular domains located N-terminally to the TMD can further include an additional domain, for example a membrane localization signal such as a CD8α signal, a detectable marker such as a myc tag or his tag, and the like. In some embodiments, the chimeric receptors further comprise one or more additional proteolytic cleavage sites. In some embodiments, the chimeric receptors do not comprise an additional proteolytic cleavage site. In some embodiments, the chimeric receptors further comprise one or more glycosylation sites. In some embodiments, the chimeric receptors do not comprise a glycosylation site. In some embodiments, the chimeric receptors do not comprise a hinge domain for promoting oligomerization of the chimeric polypeptide via intermolecular disulfide bonding.

[0099] In some embodiments, the chimeric receptors further comprise elements of the highly conserved ROBO cell surface receptors. In some embodiments, the chimeric receptors disclosed comprise, from N-terminus to C-terminus: (a) an extracellular ligand binding domain having a binding affinity for a selected ligand; (b) a ROBO domain comprising a fibronectin repeat; (c) a TMD including one or more ligand-inducible proteolytic cleavage sites; and (d) an ICD including a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site in the TMD, and wherein the chimeric polypeptide does not include a sequence from a Notch receptor.

[0100] In some embodiments, the chimeric receptors further comprise an extracellular oligomerization domain (*e.g.*, a hinge domain) to promote oligomerization, *e.g.*, dimerization, trimerization, or higher order multimers of the chimeric receptor. In some embodiments, the chimeric receptors disclosed comprise, from N-terminus to C-terminus: (a) an extracellular ligand binding domain having a binding affinity for a selected ligand; (b) a hinge domain; (c) a TMD including one or more ligand-inducible proteolytic cleavage sites; and (d) an ICD including a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site in the TMD, and wherein the chimeric polypeptide does not include a sequence from a Notch receptor.

[0101] In some embodiments, the hinge domain includes polypeptide motifs capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding. In some embodiments, a chimeric receptor disclosed herein includes, from N-terminus to C-terminus: (a) an extracellular ligand binding domain having a binding affinity for a selected ligand; (b) a hinge domain capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding; (c) a TMD comprising one or more ligand-inducible proteolytic cleavage sites; and (d) an ICD comprising a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at a ligand-inducible proteolytic cleavage sites in the TMD, and wherein the chimeric polypeptide does not comprise a sequence from a Notch receptor.

[0102] Chimeric receptors of the present disclosure can be chimeric polypeptides of any length, including chimeric polypeptides that are generally between about 100 amino acids (aa) to about 1000 aa, *e.g.*, from about 100 aa to about 200 aa, from about 150 aa to about 250 aa, from about 200 aa to about 300 aa, from about 250 aa to about 350 aa, from about 300 aa to about 400 aa, from about 350 aa to about 450 aa, from about 400 aa to about 500 aa in length. In some embodiments, the disclosed chimeric polypeptides are generally between about 400 aa to about 450 aa, from about 450 aa to about 500 aa, from about 500 aa to about 550 aa, from about 550 aa to about 600 aa, from about 600 aa to about 650 aa, from about 650 aa to about 700 aa, from about 700 aa to about 750 aa, from about 750 aa to about 800 aa, from about 800 aa to about 850 aa, from about 850 aa to about 900 aa, from about 900 aa to about 950 aa, or from about 950 aa to about 1000 aa in length. In some cases, the chimeric polypeptides of the present disclosure have a length of from about 300 aa to about 400 aa. In some cases, the chimeric polypeptides of the present disclosure have a length of from 300 aa to 350 aa. In some cases, the chimeric polypeptides of the present disclosure have a length of from 300 aa to 325 aa. In some cases, the chimeric polypeptides of the present disclosure have a length of from 350 aa to 400 aa. In some cases, the chimeric polypeptides of the present disclosure have a length of from 750 aa to 850 aa.

[0103] In some embodiments, the chimeric receptors of the disclosure include: (a) an extracellular ligand-binding domain (b) a linking sequence including an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 157-161; (c) a TMD including an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192; (d) an STS including an amino acid sequence having at about least 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156; and (e) an ICD comprising a transcriptional regulator. In some embodiments, the chimeric receptor of the disclosure include: (a) a linking sequence including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NOS: 157-161; (b) a TMD including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192; and (c) an STS including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NO: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the chimeric receptors of the disclosure include: (a) a linking sequence including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NO: 157-161; (b) a transmembrane domain including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NO: 1-84, 178, 182-185, and 190-192; and (c) an STS including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156.

[0104] In some embodiments, the chimeric polypeptides of the disclosure include an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to a chimeric receptor disclosed herein, *e.g.*, those described in Table 1. Accordingly, in some embodiments, the chimeric polypeptides of the disclosure include an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 197-248 in the Sequence Listing. In some embodiments, the chimeric polypeptides of the disclosure include an amino acid sequence having at least about 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 197-248. In some embodiments, chimeric polypeptides of the disclosure include an amino acid sequence having at least about 95% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 197-248. In some embodiments, the chimeric polypeptides of the disclosure include an amino acid sequence having at least about 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 197-248. In some embodiments, the chimeric polypeptides of the disclosure include an amino acid sequence having at least about 100% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 197-248, wherein one, two, three, four, or five of the amino acid residues in the amino acid sequence is/are substituted by a different amino acid residue.

<u>**Nucleic Acid Molecules**</u>

[0105] In one aspect, some embodiments of the disclosure relate to nucleic acid molecules comprising nucleotide sequences encoding the chimeric polypeptides and Notch receptors of the disclosure, including expression cassettes, and expression vectors containing these nucleic acid molecules operably linked to heterologous nucleic acid sequences such as, for example, regulatory sequences which direct *in vivo* expression of the receptor in a host cell.

[0106] Nucleic acid molecules of the present disclosure can be nucleic acid molecules of any length, including nucleic acid molecules that are generally between about 5 Kb and about 50 Kb, for example between about 5 Kb and about 40 Kb, between about 5 Kb and about 30 Kb, between about 5 Kb and about 20 Kb, or between about 10 Kb and about 50 Kb, for example between about 15 Kb to 30 Kb, between about 20 Kb and about 50 Kb, between about 20 Kb and about 40 Kb, about 5 Kb and about 25 Kb, or about 30 Kb and about 50 Kb.

[0107] In some embodiments, the nucleic acid molecules comprise a nucleotide sequence encoding a chimeric receptor comprising, from N-terminus to C-terminus: (a) an extracellular ligand binding domain having a binding affinity for a selected ligand; (b) a linking sequence having: (i) at least about 80% sequence identity to a polypeptide hinge domain; or (ii) at least about 80% sequence identity to a ROBO1 JMD including at least one fibronectin (Fn) repeat; (c) a TMD having at least about 80% sequence identity to the transmembrane domain of a Type 1 transmembrane receptor comprising one or more ligand-inducible proteolytic cleavage sites; and (d) an ICD comprising a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site between the transcriptional regulator and the linking sequence, and wherein the chimeric polypeptide does not comprise a sequence from a Notch receptor.

[0108] In some embodiments, the nucleotide sequence is incorporated into an expression cassette or an expression vector. It will be understood that an expression cassette generally includes a construct of genetic material that contains coding sequences and enough regulatory information to direct proper transcription and/or translation of the coding sequences in a recipient cell, *in vivo* and/or *ex vivo*. Generally, the expression cassette may be inserted into a vector for targeting to a desired host cell or tissue and/or into an individual. Thus, in some embodiments, an expression cassette of the disclosure comprises a nucleotide sequence encoding a chimeric polypeptide operably linked to expression control elements sufficient to guide expression of the cassette *in vivo*. In some embodiments, the expression control element comprises a promoter and/or an enhancer and optionally, any or a combination of other nucleic acid sequences capable of effecting transcription and/or translation of the coding sequence.

[0109] In some embodiments, the nucleotide sequence is incorporated into an expression vector. It will be understood by one skilled in the art that the term "vector" generally refers to a recombinant polynucleotide construct designed for transfer between host cells, and that may be used for the purpose of transformation, *e.g.*, the introduction of heterologous DNA into a host cell. As such, in some embodiments, the vector can be a replicon, such as a plasmid, phage, or cosmid, into which another DNA segment may be inserted so as to bring about the replication of the inserted segment. In some embodiments, the expression vector can be an integrating vector.

[0110] In some embodiments, the expression vector can be a viral vector. As will be appreciated by one of skill in the art, the term "viral vector" is widely used to refer either to a nucleic acid molecule (*e.g.*, a transfer plasmid) that includes virus-derived nucleic acid elements that generally facilitate transfer of the nucleic acid molecule or integration into the genome of a cell or to a viral particle that mediates nucleic acid transfer. Viral particles will generally include various viral components and sometimes also host cell components in addition to nucleic acid(s). The term viral vector may refer either to a virus or viral particle capable of transferring a nucleic acid into a cell or to the transferred nucleic acid itself. Viral vectors and transfer plasmids contain structural and/or functional genetic elements that are primarily derived from a virus. The term "retroviral vector" refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from a retrovirus. The term "lentiviral vector" refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, including LTRs that are primarily derived from a lentivirus. In some embodiments, a nucleic acid molecule encoding a chimeric receptor of the disclosure can be incorporated into one or more lentiviral vector constructs. In some embodiments, a nucleic acid molecule encoding a chimeric receptor of the disclosure can be incorporated into a single lentiviral vector construct. In some embodiments, a nucleic acid molecule encoding a chimeric receptor of the disclosure can be incorporated into two, three, four, five, or more lentiviral vector constructs.

[0111] In some embodiments, the recombinant nucleic acids encode a polypeptide with an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to a chimeric receptor disclosed herein. In some embodiments, the nucleic acid molecules encode a chimeric polypeptide comprising: (a) a linking sequence including an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 157-161; (b) a transmembrane domain including an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192; and (c) an STS including an amino acid sequence having at least about 80%, 90%, 95%, 96%, 97, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the nucleic acid molecules encode a chimeric polypeptide comprising: (a) a linking sequence including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NO: 157-161; (b) a transmembrane domain including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192; and (c) an STS including an amino acid sequence having at least about 90% sequence identity to any one of SEQ ID NO: 89, 92, 108, 115, 138, 146, and 156. In some embodiments, the nucleic acid molecules encode a chimeric polypeptide comprising: (a) a linking sequence including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NOS: 157-161; (b) a transmembrane domain including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192; and (c) an STS including an amino acid sequence having at least about 95% sequence identity to any one of SEQ ID NOS: 89, 92, 108, 115, 138, 146, and 156.

[0112] The nucleic acid sequences encoding the chimeric receptors can be optimized for expression in the host cell of interest. For example, the G-C content of the sequence can be adjusted to levels average for a given cellular host, as calculated by reference to known genes expressed in the host cell. Methods for codon optimization are known in the art. Codon usages within the coding sequence of the chimeric receptor disclosed herein can be optimized to enhance expression in the host cell, such that about 1%, about 5%, about 10%, about 25%, about 50%, about 75%, or up to 100% of the codons within the coding sequence have been optimized for expression in a particular host cell.

[0113] Some embodiments disclosed herein relate to vectors or expression cassettes including a recombinant nucleic acid molecule encoding the chimeric receptors disclosed herein. The expression cassette generally contains coding sequences and sufficient regulatory information to direct proper transcription and/or translation of the coding sequences in a recipient cell, *in vivo* and/or *ex vivo*. The expression cassette may be inserted into a vector for targeting to a desired host cell and/or into an individual. An expression cassette can be inserted into a plasmid, cosmid, virus, autonomously replicating polynucleotide molecule, or bacteriophage, as a linear or circular, single-stranded or double-stranded, DNA or RNA polynucleotide, derived from any source, capable of genomic integration or autonomous replication, including a nucleic acid molecule where one or more nucleic acid sequences has been linked in a functionally operative manner, i.e., operably linked.

[0114] Also provided herein are vectors, plasmids, or viruses containing one or more of the nucleic acid molecules encoding any chimeric receptor disclosed herein. The nucleic acid molecules can be contained within a vector that is capable of directing their expression in, for example, a cell that has been transformed/transduced with the vector. Suitable vectors for use in eukaryotic and prokaryotic cells are known in the art and are commercially available, or readily prepared by a skilled artisan. See for example, Sambrook, J., & Russell, D. W. (2012). *Molecular Cloning: A Laboratory Manual* (4th ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory and Sambrook, J., & Russel, D. W. (2001). *Molecular Cloning: A Laboratory Manual* (3rd ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory (jointly referred to herein as “Sambrook”); Ausubel, F. M. (1987). *Current Protocols in Molecular Biology*. New York, NY: Wiley (including supplements through 2014); Bollag, D. M. et al. (1996). *Protein Methods*. New York, NY: Wiley-Liss; Huang, L. et al. (2005). *Nonviral Vectors for Gene Therapy*. San Diego: Academic Press; Kaplitt, M. G. et al. (1995). *Viral Vectors: Gene Therapy and Neuroscience Applications*. San Diego, CA: Academic Press; Lefkovits, I. (1997). *The Immunology Methods Manual: The Comprehensive Sourcebook of Techniques*. San Diego, CA: Academic Press; Doyle, A. et al. (1998). *Cell and Tissue Culture: Laboratory Procedures in Biotechnology*. New York, NY: Wiley; Mullis, K. B., Ferré, F. & Gibbs, R. (1994). *PCR: The Polymerase Chain Reaction*. Boston: Birkhauser Publisher; Greenfield, E. A. (2014). *Antibodies: A Laboratory Manual* (2nd ed.). New York, NY: Cold Spring Harbor Laboratory Press; Beaucage, S. L. et al. (2000). *Current Protocols in Nucleic Acid Chemistry*. New York, NY: Wiley, (including supplements through 2014); and Makrides, S. C. (2003). *Gene Transfer and Expression in Mammalian Cells*. Amsterdam, NL: Elsevier Sciences B.V., the disclosures of which are incorporated herein by reference.

[0115] DNA vectors can be introduced into eukaryotic cells via conventional transformation or transfection techniques. Suitable methods for transforming or transfecting host cells can be found in Sambrook et al. (2012, *supra*) and other standard molecular biology laboratory manuals, such as, calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction, nucleoporation, hydrodynamic shock, and infection.

[0116] Viral vectors that can be used in the disclosure include, for example, retrovirus vectors, adenovirus vectors, and adeno-associated virus vectors, lentivirus vectors, herpes virus, simian virus 40 (SV40), and bovine papilloma virus vectors (see, for example, Gluzman (Ed.), *Eukaryotic Viral Vectors*, CSH Laboratory Press, Cold Spring Harbor, N.Y.). For example, a chimeric receptor as disclosed herein can be produced in a eukaryotic host, such as a mammalian cells (*e.g.*, COS cells, NIH 3T3 cells, or HeLa cells). These cells are available from many sources, including the American Type Culture Collection (Manassas, Va.). In selecting an expression system, care should be taken to ensure that the components are compatible with one another. Artisans or ordinary skill are able to make such a determination. Furthermore, if guidance is required in selecting an expression system, skilled artisans may consult P. Jones, "Vectors: Cloning Applications", John Wiley and Sons, New York, N.Y., 2009).

[0117] The nucleic acid molecules provided can contain naturally occurring sequences, or sequences that differ from those that occur naturally but encode the same gene product because the genetic code is degenerate. These nucleic acid molecules can consist of RNA or DNA (for example, genomic DNA, cDNA, or synthetic DNA, such as that produced by phosphoramidite-based synthesis), or combinations or modifications of the nucleotides within these types of nucleic acids. In addition, the nucleic acid molecules can be double-stranded or single-stranded (*e.g.*, comprising either a sense or an antisense strand).

[0118] The nucleic acid molecules are not limited to sequences that encode polypeptides (*e.g.*, antibodies); some or all of the non-coding sequences that lie upstream or downstream from a coding sequence (*e.g.*, the coding sequence of a chimeric receptor) can also be included. Those of ordinary skill in the art of molecular biology are familiar with routine procedures for isolating nucleic acid molecules. They can, for example, be generated by treatment of genomic DNA with restriction endonucleases, or by the polymerase chain reaction (PCR). In the event the nucleic acid molecule is a ribonucleic acid (RNA), transcripts can be produced, for example, by *in vitro* transcription.

Recombinant Cells and Cell Cultures

[0119] The nucleic acid of the present disclosure can be introduced into a host cell, such as a human T lymphocyte, to produce a recombinant cell containing the nucleic acid molecule. Accordingly, some embodiments of the disclosure relate to methods for making recombinant cells, including the steps of: (a) providing a cell capable of protein expression and (b) contacting the provided cell with any of the recombinant nucleic acids described herein.

[0120] Introduction of the nucleic acid molecules of the disclosure into cells can be achieved by viral infection, transfection, conjugation, protoplast fusion, lipofection, electroporation, nucleofection, calcium phosphate precipitation, polyethyleneimine (PEI)-mediated transfection, DEAE-dextran mediated transfection, liposome-mediated transfection, particle gun technology, calcium phosphate precipitation, direct micro-injection, nanoparticle-mediated nucleic acid delivery, and the like.

[0121] Accordingly, in some embodiments, the nucleic acid molecules are delivered to cells by viral or non-viral delivery vehicles known in the art. For example, the nucleic acid molecule can be stably integrated in the host genome, or can be episomally replicating, or present in the recombinant host cell as a mini-circle expression vector for a stable or transient expression. Accordingly, in some embodiments disclosed herein, the nucleic acid molecule is maintained and replicated in the recombinant host cell as an episomal unit. In some embodiments, the nucleic acid molecule is stably integrated into the genome of the recombinant cell. Stable integration can be completed using classical random genomic recombination techniques or with more precise genome editing techniques such as using guide RNA directed CRISPR/Cas9, or DNA-guided endonuclease genome editing NgAgo (*Natronobacterium gregoryi* Argonaute), or TALENs genome editing (transcription activator-like effector nucleases). In some embodiments, the nucleic acid molecule present in the recombinant host cell as a mini-circle expression vector for a stable or transient expression.

[0122] The nucleic acid molecules can be encapsulated in a viral capsid or a lipid nanoparticle. For example, introduction of nucleic acids into cells may be achieved by viral transduction. In a non-limiting example, adeno-associated virus (AAV) is a non-enveloped virus that can be engineered to deliver nucleic acids to target cells via viral transduction. Several AAV serotypes have been described, and all of the known serotypes can infect cells from multiple diverse tissue types. AAV is capable of transducing a wide range of species and tissues *in vivo* with no evidence of toxicity, and it generates relatively mild innate and adaptive immune responses.

[0123] Lentiviral systems are also suitable for nucleic acid delivery and gene therapy via viral transduction. Lentiviral vectors offer several attractive properties as gene-delivery vehicles, including: (i) sustained gene delivery through stable vector integration into host genome; (ii) the ability to infect both dividing and non-dividing cells; (iii) broad tissue tropisms, including important gene- and cell-therapy-target cell types; (iv) no expression of viral proteins after vector transduction; (v) the ability to deliver complex genetic elements, such as polycistronic or intron-containing sequences; (vi) potentially safer integration site profile; and (vii) a relatively easy system for vector manipulation and production.

[0124] In some embodiments, host cells can be genetically engineered (*e.g.*, transduced, transformed, or transfected) with, for example, a vector comprising a nucleic acid sequence encoding a chimeric receptor as described herein, either a virus-derived expression vector or a vector for homologous recombination further comprising nucleic acid sequences homologous to a portion of the genome of the host cell. Host cells can be either untransformed cells or cells that have already been transfected with one or more nucleic acid molecules.

[0125] In some embodiments, the recombinant cell is a prokaryotic cell or a eukaryotic cell. In some embodiments, the cell is transformed *in vivo*. In some embodiments, the cell is transformed *ex vivo*. In some embodiments, the cell is transformed *in vitro*. In some embodiments, the recombinant cell is a eukaryotic cell. In some embodiments, the recombinant cell is an animal cell. In some embodiments, the animal cell is a mammalian cell. In some embodiments, the animal cell is a human cell. In some embodiments, the cell is a non-human primate cell. In some embodiments, the mammalian cell is an immune cell, a neuron, an epithelial cell, and endothelial cell, or a stem cell. In some embodiments, the recombinant cell is an immune system cell, *e.g.*, a lymphocyte (*e.g.*, a T cell or NK cell), or a dendritic cell. In some embodiments, the immune cell is a B cell, a monocyte, a natural killer (NK) cell, a basophil, an eosinophil, a neutrophil, a dendritic cell, a macrophage, a regulatory T cell, a helper T cell, a cytotoxic T cell, or other T cell. In some embodiments, the immune system cell is a T lymphocyte.

[0126] In some embodiments, the cell is a stem cell. In some embodiments, the cell is a hematopoietic stem cell. In some embodiments of the cell, the cell is a lymphocyte. In some embodiments, the cell is a precursor T cell or a T regulatory (Treg) cell. In some embodiments, the cell is a CD34+, CD8+, or a CD4+ cell. In some embodiments, the cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells, and bulk CD8+ T cells. In some embodiments of the cell, the cell is a CD4+ T helper lymphocyte cell selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells. In some embodiments, the cell can be obtained by leukapheresis performed on a sample obtained from a human subject.

[0127] In some embodiments, the recombinant cell further includes a second nucleic acid molecule as disclosed herein, wherein the first nucleic acid molecule and the second nucleic acid molecule do not have the same sequence. In some embodiments, the recombinant cell further includes a second chimeric polypeptide as disclosed herein, wherein the first chimeric polypeptide and the second chimeric polypeptide do not have the same sequence. In some embodiments, the first chimeric polypeptide modulates the expression and/or activity of the second chimeric polypeptide.

[0128] In some embodiments, the recombinant cell further includes an expression cassette encoding a protein of interest operably linked to a promoter, wherein expression of the protein of interest is modulated by the transcriptional regulator encoded by the chimeric receptor. In some embodiments, the protein of interest is heterologous to the recombinant cell. In principle, there are no particular limitations with regard to selecting proteins to target for modulation of expression by the transcriptional regulator encoded by the chimeric receptor. Non-limiting examples of proteins suitable for the regulation by the compositions and methods disclosed herein include cytokines, cytotoxins, chemokines, immunomodulators, pro-apoptotic factors, anti-apoptotic factors, hormones, differentiation factors, dedifferentiation factors, immune cell receptors, or reporter genes. In some embodiments, the immune cell receptor comprises a T-cell receptor (TCR). A TCR generally comprises two polypeptides (*e.g.*, polypeptide chains), such as an α-chain of a TCR, a β-chain of a TCR, a γ-chain of a TCR, a δ-chain of a TCR, or a combination thereof. Such polypeptide chains of TCRs are known in the art. In some embodiments, the immune cell receptor comprises a chimeric antigen receptor (CAR). Methods for CAR design, delivery and expression in T cells, and the manufacturing of clinical-grade CAR-T cell populations are known in the art. See, for example, Lee *et al.*, *Clin Cancer Res* (2012) **18**(10):2780-90, hereby incorporated by reference in its entirety. In some embodiments, the expression cassette encoding the protein of interest is incorporated into the same nucleic acid molecule that encodes the chimeric receptor of the disclosure. In some embodiments, the expression cassette encoding the protein of interest is incorporated into a second expression vector that is separate from the nucleic acid molecule encoding the chimeric receptor of the disclosure.

[0129] In another aspect, provided herein are various cell cultures including at least one recombinant cell as disclosed herein, and a culture medium. Generally, the culture medium can be any one of suitable culture media for the cell cultures described herein. Techniques for transforming a wide variety of the above-mentioned host cells and species are known in the art and described in the technical and scientific literature. Accordingly, cell cultures including at least one recombinant cell as disclosed herein are also within the scope of this application. Methods and systems suitable for generating and maintaining cell cultures are known in the art.

Pharmaceutical Compositions

[0130] In some embodiments, the nucleic acids, and recombinant cells of the disclosure can be incorporated into compositions, including pharmaceutical compositions. Such compositions generally include the nucleic acids, and/or recombinant cells, and a pharmaceutically acceptable excipient, *e.g.*, a carrier.

[0131] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™. (BASF, Parsippany, N.J.), or phosphate buffered saline (PBS). In all cases, the composition should be sterile and should be fluid to the extent that it can be administered by syringe. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants, *e.g.*, sodium dodecyl sulfate. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be generally to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and/or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0132] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0133] In some embodiments, the chimeric polypeptides and SynRIPRs of the disclosure can also be administered by transfection or infection using methods known in the art, including but not limited to the methods described in McCaffrey et al. (*Nature* (2002) **418**:6893), Xia et al. (*Nature Biotechnol* (2002) **20**:1006-10), or Putnam (*Am J Health Syst Pharm* (1996) **53**:151-60, erratum at *Am J Health Syst Pharm* (1996) **53**:325).

METHODS OF THE DISCLOSURE

[0134] Administration of any one or more of the therapeutic compositions described herein, *e.g.*, nucleic acids, recombinant cells, and pharmaceutical compositions, can be used to treat individuals having a disease, such as cancers and chronic infections. In some embodiments, the nucleic acids, recombinant cells, and pharmaceutical compositions are incorporated into therapeutic compositions for use in methods of treating an individual who has, who is suspected of having, or who may be at high risk for developing one or more autoimmune disorders or diseases associated with checkpoint inhibition. Exemplary autoimmune disorders and diseases can include, without limitation, celiac disease, type 1 diabetes, Graves' disease, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.

[0135] Accordingly, in one aspect, provided herein are methods for inhibiting an activity of a target cell in an individual, the methods comprising the step of administering to the individual a first therapy including one or more of the nucleic acids, recombinant cells, and pharmaceutical compositions provided herein, wherein the first therapy inhibits an activity of the target cell. For example, an activity of the target cell may be inhibited if its proliferation is reduced, if its pathologic or pathogenic behavior is reduced, if it is destroyed or killed, or the like. Inhibition includes a reduction of the measured quantity of at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, the methods include administering to the individual an effective number of the recombinant cell as disclosed herein, wherein the recombinant cell inhibits the target cell in the individual. Generally, the target cell of the disclosed methods can be any cell such as, for example an acute myeloma leukemia cell, an anaplastic lymphoma cell, an astrocytoma cell, a B-cell cancer cell, a breast cancer cell, a colon cancer cell, an ependymoma cell, an esophageal cancer cell, a glioblastoma cell, a glioma cell, a leiomyosarcoma cell, a liposarcoma cell, a liver cancer cell, a lung cancer cell, a mantle cell lymphoma cell, a melanoma cell, a neuroblastoma cell, a non-small cell lung cancer cell, an oligodendroglioma cell, an ovarian cancer cell, a pancreatic cancer cell, a peripheral T-cell lymphoma cell, a renal cancer cell, a sarcoma cell, a stomach cancer cell, a carcinoma cell, a mesothelioma cell, or a sarcoma cell. In some embodiments, the target cell is a pathogenic cell.

[0136] In another aspect, provided herein are methods of treating a disease in an individual in need thereof, the methods comprising a step of administering to the individual a first therapy including one or more of chimeric polypeptides, SynRIPRs, nucleic acids, recombinant cells, or pharmaceutical compositions provided herein, wherein the first therapy treats the disease in the individual. In some embodiments, the methods include administering to the individual a first therapy including an effective number of the recombinant cells provided herein, wherein the recombinant cells treat the disease.

[0137] In another aspect, provided herein are methods for assisting in the treatment of a disease in an individual in need thereof, the methods comprising the steps of administering to the individual a first therapy comprising one or more recombinant nucleic acids, recombinant cells, or pharmaceutical compositions as disclosed herein, and administering to the individual a second therapy, wherein the first and second therapies together treat the disease in the individual. In some embodiments, the methods include administering to the individual a first therapy including an effective number of the recombinant cells as disclosed herein, wherein the recombinant cells treat the disease.

Administration of recombinant cells to an individual

[0138] In some embodiments, the methods involve administering an effective amount or number of the recombinant cells of the disclosure to an individual who is in need of such method. This administering step can be accomplished using any method of implantation known in the art. For example, the recombinant cells of the disclosure can be injected directly into the individual's bloodstream by intravenous infusion or otherwise administered to the individual.

[0139] The terms "administering", "introducing", and "transplanting" are used interchangeably herein to refer to methods of delivering recombinant cells expressing the chimeric receptors provided herein to an individual. In some embodiments, the methods comprise administering recombinant cells to an individual by a method or route of administration that results in at least partial localization of the introduced cells at a desired site such that a desired effect(s) is/are produced. The recombinant cells or their differentiated progeny can be administered by any appropriate route that results in delivery to a desired location in the individual where at least a portion of the administered cells or components of the cells remain viable. The period of viability of the cells after administration to an individual can be as short as a few hours, *e.g.*, twenty-four hours, to a few days, to as long as several years, or even long-term engraftment for the life time of the individual.

[0140] When provided prophylactically, in some embodiments, the recombinant cells described herein are administered to an individual in advance of any symptom of a disease or condition to be treated. Accordingly, in some embodiments the prophylactic administration of a recombinant stem cell population serves to prevent the occurrence of symptoms of the disease or condition.

[0141] When provided therapeutically in some embodiments, recombinant stem cells are provided at (or after) the onset of a symptom or indication of a disease or condition, *e.g.*, upon the onset of disease or condition.

[0142] For use in the various embodiments described herein, an effective amount of recombinant cells as disclosed herein, can be at least 10^2 cells, at least 5×10^2 cells, at least 10^3 cells, at least 5×10^3 cells, at least 10^4 cells, at least 5×10^4 cells, at least 10^5 cells, at least 2×10^5 cells, at least 3×10^5 cells, at least 4×10^5 cells, at least 5×10^5 cells, at least 6×10^5 cells, at least 7×10^5 cells, at least 8×10^5 cells, at least 9×10^5 cells, at least 1×10^6 cells, at least 2×10^6 cells, at least 3×10^6 cells, at least 4×10^6 cells, at least 5×10^6 cells, at least 6×10^6 cells, at least 7×10^6 cells, at least 8×10^6 cells, at least 9×10^6 cells, or multiples thereof. The recombinant cells can be derived from one or more donors or can be obtained from an autologous source (i.e., the human subject being treated). In some embodiments, the recombinant cells are expanded in culture prior to administration to an individual in need thereof.

[0143] In some embodiments, the delivery of a composition comprising recombinant cells (i.e., a composition comprising a plurality of recombinant cells expressing any of the chimeric receptors provided herein) into an individual by a method or route results in at least partial localization of the cell composition at a desired site. A cell composition can be administered by any appropriate route that results in effective treatment in the individual, *e.g.*, administration results in delivery to a desired location in the individual where at least a portion of the composition delivered, *e.g.*, at least 1×10^4 cells, is delivered to the desired site for a period of time. Modes of administration include injection, infusion, instillation, and the like. "Injection" includes, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intracerebrospinal, and intrasternal injection and infusion. In some embodiments, the route is intravenous. For the delivery of cells, administration by injection or infusion can be made.

[0144] In some embodiments, the recombinant cells are administered systemically, in other words a population of recombinant cells are administered other than directly into a target site, tissue, or organ, such that it enters, instead, the individual's circulatory system and, thus, is subject to metabolism and other like processes.

[0145] The efficacy of a treatment with a composition for the treatment of a disease or condition can be determined by the skilled clinician. However, one skilled in the art will appreciate that a treatment is considered effective treatment if any one or all of the signs or symptoms or markers of disease are improved or ameliorated. Efficacy can also be measured by failure of an individual to worsen as assessed by hospitalization or need for medical interventions (*e.g.*, progression of the disease is halted or at least slowed). Methods of measuring these indicators are known to those of skill in the art and/or described herein. Treatment includes any treatment of a disease in an individual or an animal (some non-limiting examples include a human, or a mammal) and includes: (1) inhibiting disease progression, *e.g.*, arresting, or slowing the progression of symptoms; or (2) relieving the disease, *e.g.*, causing regression of symptoms; and (3) preventing or reducing the likelihood of the development of symptoms.

[0146] As discussed above, a therapeutically effective amount includes an amount of a therapeutic composition that is sufficient to promote a particular effect when administered to an individual, such as one who has, is suspected of having, or is at risk for a disease. In some embodiments, an effective amount includes an amount sufficient to prevent or delay the development of a symptom of the disease, alter the course of a symptom of the disease (for example but not limited to, slow the progression of a symptom of the disease), or reverse a symptom of the disease. It is understood that for any given case, an appropriate effective amount can be determined by one of ordinary skill in the art using routine experimentation.

[0147] The efficacy of a treatment including a disclosed therapeutic composition for the treatment of disease can be determined by the skilled clinician. However, a treatment is considered effective if at least any one or all of the signs or symptoms of disease are improved or ameliorated. Efficacy can also be measured by failure of an individual to worsen as assessed by hospitalization or need for medical interventions (*e.g.*, progression of the disease is halted or at least slowed). Methods of measuring these indicators are known to those of skill in the art and/or described herein. Treatment includes any treatment of a disease in an individual or an animal (some non-limiting examples include a human, or a mammal) and includes: (1) inhibiting the disease, *e.g.*, arresting, or slowing the progression of symptoms; (2) relieving the disease, *e.g.*, causing regression of symptoms; or (3) preventing or reducing the likelihood of the development of symptoms.

[0148] In some embodiments, the individual is a mammal. In some embodiments, the mammal is human. In some embodiments, the individual has or is suspected of having a disease associated with inhibition of cell signaling mediated by a cell surface ligand or antigen. The diseases suitable for being treated by the compositions and methods of the disclosure include, but are not limited to, cancers, autoimmune diseases, inflammatory diseases, and infectious diseases. In some embodiments, the disease is a cancer or a chronic infection.

[0149] Methods for CAR design, delivery and expression in T cells, and the manufacturing of clinical-grade CAR-T cell populations are known in the art. See, for example, Lee *et al., Clin Cancer Res* (2012) **18**(10):2780-90, hereby incorporated by reference in its entirety. For example, the engineered CARs may be introduced into cells, e.g., T cells, using retroviruses, which efficiently and stably integrate a nucleic acid sequence encoding the chimeric antigen receptor into the target cell genome. An exemplary method is described in Examples 4 and 7 below.

[0150] Other methods known in the art include, but are not limited to, lentiviral transduction, transposon-based systems, direct RNA transfection, and CRISPR/Cas systems (*e.g.*, type I, type II, or type III systems using a suitable Cas protein).

[0151] In some embodiments, a recombinant adeno-associated virus (AAV) vector can be used for delivery. Techniques to produce rAAV particles, in which an AAV genome to be packaged that includes the polynucleotide to be delivered, rep and cap genes, and helper virus functions are provided to a cell are standard in the art. Production of rAAV requires that the following components are present within a single cell (denoted herein as a packaging cell): a rAAV genome, AAV rep and cap genes separate from (*e.g.*, not in) the rAAV genome, and helper virus functions. The AAV rep and cap genes can be from any AAV serotype for which recombinant virus can be derived, and can be from a different AAV serotype than the rAAV genome ITRs, including, but not limited to, AAV serotypes AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12, AAV-13 and AAV rh.74. Production of pseudotyped rAAV is disclosed in, for example, international patent application publication number WO 01/83692.

[0152] The CAR-T cells, once they have been expanded *ex vivo* in response to, for example, an autoimmune disease antigen, can be reinfused into the subject in a therapeutically effective amount.

[0153] The precise amount of CAR T cells to be administered can be determined by a physician with consideration of individual differences in age, weight, extent of disease and condition of the subject.

[0154] Administration of T cell therapies may be defined by number of total cells per infusion or number of cells per kilogram of body weight, especially for pediatric subjects (*e.g.*, patients). As T cells replicate and expand after transfer, the administered cell dose may not resemble the final steady-state number of cells. In some embodiments, a pharmaceutical composition including the CAR T cells of the present disclosure may be administered at a dosage of 10^4 to 10^{10} total cells. In another embodiment, a pharmaceutical composition including the CAR T cells of the present disclosure may be administered at a dosage of 10^3 to 10^8 cells/kg body weight, including all integer values within those ranges.

[0155] Compositions including the CAR T cells of the present disclosure may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are known in the art (see, for example, Rosenberg *et al.*, *New Engl J Med*, (1988) **319**:1676). The optimal dosage and treatment regimen for a particular subject can be determined by one skilled in the art by monitoring the subject for signs of disease and adjusting the treatment accordingly.

<u>*Additional therapies*</u>

[0156] As discussed above, the recombinant cells, and pharmaceutical compositions described herein can be administered in combination with one or more additional therapeutic agents such as, for example, chemotherapeutics or anti-cancer agents or anti-cancer therapies. Administration "in combination with" one or more additional therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order. In some embodiments, the one or more additional therapeutic agents, chemotherapeutics, anti-cancer agents, or anti-cancer therapies is selected from the group consisting of chemotherapy, radiotherapy, immunotherapy, hormonal therapy, toxin therapy, and surgery. "Chemotherapy" and "anti-cancer agent" are used interchangeably herein. Various classes of anti-cancer agents can be used. Non-limiting examples include: alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, podophyllotoxin, antibodies (*e.g.*, monoclonal or polyclonal), tyrosine kinase inhibitors (*e.g.*, imatinib mesylate (Gleevec® or Glivec®)), hormone treatments, soluble receptors and other antineoplastics.

[0157] Accordingly, in some embodiments, the methods of the disclosure include administration of a composition disclosed herein to a subject individually as a single therapy (*e.g.*, monotherapy). In some embodiments, a composition of the disclosure is administered to a subject as a first therapy in combination with a second therapy. In some embodiments, the second therapy is selected from the group consisting of chemotherapy, radiotherapy, immunotherapy, hormonal therapy, toxin therapy, and surgery. In some embodiments, the first therapy and the second therapy are administered concomitantly. In some embodiments, the first therapy is administered at the same time as the second therapy. In some embodiments, the first therapy and the second therapy are administered sequentially. In some embodiments, the first therapy is administered before the second therapy. In some embodiments, the first therapy is administered after the second therapy. In some embodiments, the first therapy is administered before and/or after the second therapy. In some embodiments, the first therapy and the second therapy are administered in rotation. In some embodiments, the first therapy and the second therapy are administered together in a single formulation.

Methods for modulating an activity of a cell

[0158] In another aspect, provided herein are various methods for modulating an activity of a cell. The methods include: (a) providing a recombinant cell of the disclosure, and (b) contacting it with a selected ligand, wherein binding of the selected ligand to the extracellular binding domain induces cleavage of a ligand-inducible proteolytic cleavage site and releases the transcriptional regulator, wherein the released transcriptional regulator modulates an activity of the recombinant cell. One skilled in the art upon reading the present disclosure will appreciate that the disclosed methods can be carried out *in vivo*, *ex vivo*, or *in vitro*.

[0159] Activities of a cell that can be modulated using a method of the present disclosure include, but are not limited to, expression of a selected gene of the cell, proliferation of the cell, apoptosis of the cell, non-apoptotic death of the cell, differentiation of the cell, dedifferentiation of the cell, migration of the cell, secretion of a molecule from the cell, cellular adhesion of the cell, and cytolytic activity of the cell.

[0160] In some embodiments, the released transcriptional regulator modulates expression of a gene product of the cell. In some embodiments, the released transcriptional regulator modulates expression of a heterologous gene product in the cell. A heterologous gene product is one that is not normally produced by the cell. For example, the cell can be genetically modified with a nucleic acid comprising a nucleotide sequence encoding the heterologous gene product.

[0161] In some embodiments, the heterologous gene product is a secreted gene product. In some embodiments, the heterologous gene product is a cell surface gene product. In some cases, the heterologous gene product is a cytoplasmic gene product. In some embodiments, the released transcriptional regulator simultaneously modulates expression of two or more heterologous gene products in the cell.

[0162] In some embodiments, the heterologous gene product in the cell is selected from the group consisting of a chemokine, a chemokine receptor, a chimeric antigen receptor, a cytokine, a cytokine receptor, a differentiation factor, a growth factor, a growth factor receptor, a hormone, a metabolic enzyme, a pathogen derived protein, a proliferation inducer, a receptor, an RNA guided nuclease, a site-specific nuclease, a T cell receptor (TCR), a chimeric antigen receptor (CAR), a toxin, a toxin-derived protein, a transcriptional regulator, a transcriptional activator, a transcriptional repressor, a translation regulator, a translational activator, a translational repressor, an activating immuno-receptor, an antibody, an apoptosis inhibitor, an apoptosis inducer, an engineered T-cell receptor, an immuno-activator, an immuno-inhibitor, and an inhibiting immuno-receptor.

[0163] In some embodiments, the released transcriptional regulator modulates differentiation of the cell, and wherein the cell is an immune cell, a stem cell, a progenitor cell, or a precursor cell.

[0164] The chimeric receptors of the disclosure provide a higher degree of expression than a standard SynNotch receptor, when using identical binding domains and ICDs. In some embodiments, depending on the ligand/binding domain pair and their affinity, the SynRIPR of the disclosure can provide expression enhancement of about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, or about 50% higher than a corresponding SynNotch receptor.

[0165] Additionally, the chimeric receptors of the disclosure can provide transcriptional regulation that responds to the degree of T cell activation, independent of ligand binding. This permits additional flexibility in use, for example in cases where it is desired to enhance or suppress a T cell response when activated despite the absence of the chimeric receptor ligand.

SYSTEMS AND KITS

[0166] Also provided herein are systems and kits including the chimeric polypeptides, SynRIPRs, recombinant nucleic acids, recombinant cells, or pharmaceutical compositions provided and described herein as well as written instructions for making and using the same. For example, provided herein, in some embodiments, are systems and/or kits that include one or more of: a chimeric polypeptide as described herein, a SynRIPR as described herein, a recombinant nucleic acids as described herein, a recombinant cell as described herein, or a pharmaceutical composition as described herein. In some embodiments, the systems and/or kits of the disclosure further include one or more syringes (including pre-filled syringes) and/or catheters (including pre-filled syringes) used to administer one any of the provided chimeric polypeptides, SynRIPRs, recombinant nucleic acids, recombinant cells, or pharmaceutical compositions to an individual. In some embodiments, a kit can have one or more additional therapeutic agents that can be administered simultaneously or sequentially with the other kit components for a desired purpose, *e.g.*, for modulating an activity of a cell, inhibiting a target cancer cell, or treating a disease in an individual in need thereof.

[0167] Any of the above-described systems and kits can further include one or more additional reagents, where such additional reagents can be selected from: dilution buffers; reconstitution solutions, wash buffers, control reagents, control expression vectors, negative control polypeptides, positive control polypeptides, reagents for *in vitro* production of the chimeric receptor polypeptides.

[0168] In some embodiments, the components of a system or kit can be in separate containers. In some other embodiments, the components of a system or kit can be combined in a single container.

[0169] In some embodiments, a system or kit can further include instructions for using the components of the kit to practice the methods. The instructions for practicing the methods are generally recorded on a suitable recording medium. For example, the instructions can be printed on a substrate, such as paper or plastic, and the like. The instructions can be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or sub-packaging), and the like. The instructions can be present as an electronic storage data file present on a suitable computer readable storage medium, *e.g.*, CD-ROM, diskette, flash drive, and the like. In some instances, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source (*e.g.*, via the internet), can be provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions can be recorded on a suitable substrate.

[0170] All publications and patent applications mentioned in this disclosure are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0171] No admission is made that any reference cited herein constitutes prior art. The discussion of the references states what their authors assert, and the inventors reserve the right to challenge the accuracy and pertinence of the cited documents. It will be clearly understood that, although a number of information sources, including scientific journal articles, patent documents, and textbooks, are referred to herein; this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0172] The discussion of the general methods given herein is intended for illustrative purposes only. Other alternative methods and alternatives will be apparent to those of skill in the art upon review of this disclosure, and are to be included within the spirit and purview of this application.

EXAMPLES

[0173] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, cell biology, biochemistry, nucleic acid chemistry, and immunology, which are well known to those skilled in the art. Such techniques are explained fully in the literature cited above.

[0174] Additional embodiments are disclosed in further detail in the following examples, which are provided by way of illustration and are not in any way intended to limit the scope of this disclosure or the claims.

EXAMPLE 1

Design and construction of chimeric receptor and response element constructs

[0175] This Example describes the design and construction of a family of non-Notch regulated intramembrane proteolysis receptors (SynRIPRs) receptors. Receptors were built by fusing the CD19 scFV (Porter et al., 2011) to an extracellular domain comprised of a truncated CD8α (P01732) hinge region (Thr138 to Cys164; SEQ ID NO: 158), a transmembrane domain (TMD) and intracellular juxtamembrane domain (STS as indicated below), and a transcriptional regulator. The transcriptional regulator GAL4-VP64 used in these experiments contained a DNA domain from yeast GAL4 transcription factor fused to an activation domain VP64, which consists of a tetrameric repeat of the minimal activation domain (amino acids 437-447) of the herpes simplex protein VP16.

[0176] Detailed information for various exemplary receptors of the disclosure can be found in Table 1 below.

TABLE 1. This table provides a brief description for each of the chimeric receptors of the disclosure, their corresponding components, as well as corresponding sequence identifiers as set forth in the Sequence Listing. ECD: extracellular domain; N-JMD: N-terminal juxtamembrane domain (*i.e.*, hinge domain); TMD: transmembrane domain; STS: stop-transfer-sequence; TF: transcriptional factor.

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
pIZ343GIVV	antiCD19scFv-CD8Hinge2-Notch1TMD_GIVVLLSmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 176	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 197
pIZ343GIVVa	antiCD19scFv-CD8Hinge2-Notch1TMD_GIVVSmut-	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 177	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 198

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	Notch1STS-Gal4VP64						
pIZ373	antiCD19scFv-IgG4Hinge(NoGS Linker)-Notch1TMD-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 175	SEQ ID NO: 173	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 199
pIZ377	antiCD19scFv-CD8Hinge2-CLSTN2TMD-PTPRFSTS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 2	SEQ ID NO: 108	SEQ ID NO: 196	SEQ ID NO: 200
pIZ378	antiCD19scFv-CD8Hinge2-CLSTN2TMD-AGERSTS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 2	SEQ ID NO: 115	SEQ ID NO: 196	SEQ ID NO: 201
pIZ379	antiCD19scFv-CD8Hinge2-CLSTN2TMD-KCNE3STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 2	SEQ ID NO: 146	SEQ ID NO: 196	SEQ ID NO: 202
pTMD206	antiCD19scFv-CD8Hinge2-APPTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 6	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 203
pTMD206GV	antiCD19scFv-CD8Hinge2-APPTMD_GVmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 178	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 204
pTMD207	antiCD19scFv-CD8Hinge2-BTCTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 7	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 205
pTMD213	antiCD19scFv-CD8Hinge2-CX3CL1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 13	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 206
pTMD214	antiCD19scFv-CD8Hinge2-DCCTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 14	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 207
pTMD215	antiCD19scFv-CD8Hinge2-DLL1TMD-	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 15	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 208

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	Notch1STS-Gal4VP64						
pTMD220	antiCD19scFv-CD8Hinge2-EPCAMTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 20	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 209
pTMD225	antiCD19scFv-CD8Hinge2-ErbB4TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 25	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 210
pTMD244	antiCD19scFv-CD8Hinge2-LRP1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 44	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 211
pTMD247	antiCD19scFv-CD8Hinge2-LRP6TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 47	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 212
pTMD253	antiCD19scFv-CD8Hinge2-SCN4BTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 53	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 213
pTMD254	antiCD19scFv-CD8Hinge2-NECTIN1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 54	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 214
pTMD258	antiCD19scFv-CD8Hinge2-Notch2TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 179	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 215
pTMD259	antiCD19scFv-CD8Hinge2-Notch3TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 180	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 216
pTMD260	antiCD19scFv-CD8Hinge2-Notch4TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 181	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 217
pTMD260GV	antiCD19scFv-CD8Hinge2-Notch4TMD_GVm	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 181	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 218

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	ut-Notch1STS-Gal4VP64						
pTMD268	antiCD19scFv-CD8Hinge2-PCDHGC3TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 64	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 219
pTMD270	antiCD19scFv-CD8Hinge2-AGERTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 66	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 220
pTMD270GVLVS	antiCD19scFv-CD8Hinge2-AGERTMD_GVLVSmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 182	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 221
pTMD270LL	antiCD19scFv-CD8Hinge2-AGERTMD_LLmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 183	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 222
pTMD272	antiCD19scFv-CD8Hinge2-PTPRMTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 68	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 223
pTMD273	antiCD19scFv-CD8Hinge2-ROBO1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 69	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 224
pTMD273GV	antiCD19scFv-CD8Hinge2-ROBO1TMD_GVmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 69	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 225
pTMD273GVLLS	antiCD19scFv-CD8Hinge2-ROBO1TMD_GVLVSmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 184	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 226
pTMD276	antiCD19scFv-CD8Hinge2-SORL1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 72	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 227
pTMD277	antiCD19scFv-	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	CD8Hinge2-SORT1TMD-Notch1STS-Gal4VP64	NO: 174	NO: 158	NO: 73	NO: 193	NO: 196	NO: 228
pTMD278	antiCD19scFv-CD8Hinge2-SDC1TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 74	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 229
pTMD279	antiCD19scFv-CD8Hinge2-SDC2TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 75	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 230
pTMD280	antiCD19scFv-CD8Hinge2-SDC3TMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 76	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 231
pTMD289	antiCD19scFv-CD8Hinge2-Notch1_DrerioTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 185	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 232
pTMD290	antiCD19scFv-CD8Hinge2-Notch1_DmelanogasterTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 186	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 233
pTMD291	antiCD19scFv-CD8Hinge2-Notch1_XlaevisTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 187	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 234
pTMD292	antiCD19scFv-CD8Hinge2-Notch1_GgallusTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 188	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 235
pTMD295	antiCD19scFv-CD8Hinge2-Notch1_MmusculusTMD-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 189	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 236
pTMD297pre	antiCD19scFv-CD8Hinge-CD8aTMD-Notch1STS-	SEQ ID NO: 174	SEQ ID NO: 157	SEQ ID NO: 190	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 237

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	Gal4VP64						
pTMD297pre_GV	antiCD19scFv-CD8Hinge-CD8aTMD_GV-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 157	SEQ ID NO: 191	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 238
pTMD297pre_GVLVS	antiCD19scFv-CD8Hinge-CD8aTMD_GVLVSmut-Notch1STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 157	SEQ ID NO: 192	SEQ ID NO: 193	SEQ ID NO: 196	SEQ ID NO: 239
pSTS205	antiCD19scFv-CD8Hinge2-Notch1TMD-CSF1RSTS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 89	SEQ ID NO: 196	SEQ ID NO: 240
pSTS231	antiCD19scFv-CD8Hinge2-Notch1TMD-AGERSTS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 115	SEQ ID NO: 196	SEQ ID NO: 241
pSTS262	antiCD19scFv-CD8Hinge2-Notch1TMD-KCNE3STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 146	SEQ ID NO: 196	SEQ ID NO: 242
pSTS263	antiCD19scFv-CD8Hinge2-Notch1TMD-CDH2STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 147	SEQ ID NO: 196	SEQ ID NO: 243
pSTS266	antiCD19scFv-CD8Hinge2-Notch1TMD-BTCSTS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 150	SEQ ID NO: 196	SEQ ID NO: 244
pSTS267	antiCD19scFv-CD8Hinge2-Notch1TMD-EPHA4STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 151	SEQ ID NO: 196	SEQ ID NO: 245
pSTS268	antiCD19scFv-CD8Hinge2-Notch1TMD-IL1R2STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 101	SEQ ID NO: 196	SEQ ID NO: 246
pSTS274	antiCD19scFv-CD8Hinge2-Notch1TMD-Notch3STS-	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 194	SEQ ID NO: 196	SEQ ID NO: 247

Construct ID	Receptor Description	ECD	N-JMD	TMD	STS	TF	Full sequence
	Gal4VP64						
pIZ364	antiCD19scFv-CD8Hinge2-Notch1TMD-Notch4STS-Gal4VP64	SEQ ID NO: 174	SEQ ID NO: 158	SEQ ID NO: 173	SEQ ID NO: 195	SEQ ID NO: 196	SEQ ID NO: 248

[0177] All receptors contain an N-terminal CD8α signal peptide (MALPVTALLLPLALLLHAARP; SEQ ID NO: 162) for membrane targeting and a myc-tag (EQKLISEEDL; SEQ ID NO: 163) for suitable determination of surface expression with α-myc AF647 (Cell-Signaling #2233). For the construction of these receptors, DNA fragments coding for the amino acid sequences provided in the Sequence Listing were PCR amplified from synthesized gene fragments or plasmids containing DNA sequence for the indicated protein, and assembled using standard cloning techniques (*e.g.*, overhang PCR, fusion PCR, and In-fusion cloning) with flanking translation start and stop sequences, into a modified pHR'SIN:CSW vector (K.T. Roybal et al., *Cell* (2016) **167**(2):419-32) containing a 3-phosphoglycerate kinase (PGK) promoter for all primary T cell experiments described below.

[0178] The pHR'SIN:CSW vector was also modified to produce the response element plasmids. For this purpose, five copies of a target sequence for binding of GAL4 DBD domain (GGAGCACTGTCCTCCGAACG; SEQ ID NO: 164) were cloned 5′ to a minimal synthetic pybTATA promoter.

[0179] Also included in the response element plasmids is a PGK promoter that either constitutively drives expression of a fluorophore (mCitrine or mCherry) to suitably identify transduced T cells or a SynRIPR for single vector experimentation. For all inducible chimeric antigen-receptor (CAR) vectors, the CARs were tagged N-terminally with Flag-tag and were co-induced with GFP using a T2A element. All induced elements were cloned via a *Bam*HI site in the multiple cloning located 3' to the Gal4 response elements. All constructs were cloned via In-Fusion® cloning (Takara # 638951) according to the manufacturer's instructions.

EXAMPLE 2

Primary human T-cell isolation and culture

[0180] This Example describes the isolation and culture of primary human T cells that were subsequently used in various cell transduction experiments described in Example 3 below.

[0181] In these experiments, primary $CD4^+$ and $CD8^+$ T cells were isolated from anonymous donor blood after apheresis and enriched by negative selection using human T-cell isolation kits (human $CD4^+$ or $CD8^+$ enrichment cocktail; STEMCELL Technologies Cat #15062 and 15063). Blood was obtained from Blood Centers of the Pacific (San Francisco, CA) as approved by the University Institutional Review Board. T cells were cryopreserved in growth medium (RPMI-1640, UCSF cell culture core) with 20% human AB serum (Valley Biomedical Inc., #HP1022) and 10% DMSO. After thawing, T cells were cultured in human T cell medium containing X-VIVO™ 15 (Lonza #04-418Q), 5% Human AB serum and 10 mM neutralized N-acetyl L-Cysteine (Sigma-Aldrich #A9165) supplemented with 30 units/mL IL-2 (NCI BRB Preclinical Repository) for all experiments.

Example 3

Human T cells were stably transduced with lentiviral vectors

[0182] The Example describes a general protocol used for lentiviral transduction of human T cells.

[0183] Generally, lentiviral vectors pseudo-typed with vesicular stomatitis virus envelope G protein (VSV-G) (pantropic vectors) were produced via transfection of Lenti-X™ 293T cells (Clontech #11131D) with a pHR'SIN:CSW transgene expression vector and the viral packaging plasmids pCMVdR8.91 and pMD2.G using Mirus TransIT®-Lenti (Mirus, #MIR 6606). Generally, primary T cells were thawed the same day and, after 24 hours in culture, were stimulated with beads having anti-CD3 and anti-CD28 antibodies bound to the surface (Human T-Activator CD3/CD28 Dynabeads®, Life Technologies #11131D) at a 1:3 cell:bead ratio. At 48 hours, viral supernatant was harvested and the primary T cells were exposed to the virus for 24 hours. At Day 5 post T-cell stimulation, the beads were removed, and the T cells expanded until Day 14 when they were rested and could be used in assays. T cells were sorted for assays with a Beckton Dickinson (BD Biosciences) FACSAria™ II flow cytometer. Sorted T-cells were expanded until Day 10 for *in vivo* assays and until Day 14 for *in vitro* assays.

Example 4

In vitro SynRIPR Activation Assays

[0184] For all *in vitro* SynRIPR activation assays, 1×10^5 T cells or Jurkat T cells were co-cultured with target cells at a 1:1 ratio in 96 well round bottom plates (VWR). To exogenously activate T-cells, 100 ng/mL PMA (Sigma #P1575) or MCAM BiTEs were added to co-cultures. When activating a co-expressed ALPPL2 CAR, ALPPL2+ K562 cells were added to the co-culture in a 1:1 ratio with T cells. The cultures were analyzed at the time points indicated for reporter activation using a BD FACSymphony Fortessa X-50. All flow cytometry analysis was performed in FlowJo software (BD).

EXAMPLE 5

Cancer cell lines

[0185] This Example describes the generation of myelogenous leukemia "sender" cells expressing CD19 at equivalent levels as Daudi tumors.

[0186] The cancer cell lines used were K562 myelogenous leukemia cells (ATCC #CCL-243) and Daudi B cell lymphoblasts (ATCC #CCL-213). The K562 cells were lentivirally transduced to stably express human CD19 at equivalent levels as Daudi tumors. CD19 levels were determined by staining the cells with α-CD19 APC (Biolegend® #302212). All cell lines were sorted for expression of the transgenes.

EXAMPLE 6

Generation of reporter Jurkat T cells for screening

[0187] This Example describes the generation of reporter Jurkat T cells that were subsequent used for the screening of various synthetic receptors containing non-Notch transmembrane domains (TMD) and/or stop-transfer sequences (STS).

[0188] In these experiments, E6-1 Jurkat T cells (ATCC# TIB-152) were lentivirally transduced with a reporter plasmid carrying an inducible Gal4-driven BFP reporter gene and a constitutive expressed mCitrine reporter gene, as described previously (K.T. Roybal et al., *Cell*, 164:1-10, 2016). Reporter-positive Jurkat cells were sorted for mCitrine positive expression using a Beckton Dickinson (BD Biosciences) FACSAria™ II flow cytometer and expanded.

[0189] Lentiviral particles were produced with the receptor transgene expression vector as described previously (L. Morsut et al., *Cell* (2016) 164:780-91). Individual cultures of reporter-positive Jurkat T cells were lentivirally transduced in a 96 well plate with myc-tagged α-CD19 human SynNotch1 receptors with modified transmembrane domain (TMD) or juxtamembrane domains (STS). After viral transduction, the receptor transduction efficiency for each Jurkat cell population was measured with a BD FACSymphony Fortessa X-50 following staining with anti-myc AF647 (Cell-Signaling #2233).

EXAMPLE 7

Non-Notch synthetic regulated intramembrane proteolysis receptors (SynRIPRs)

[0190] This Example describes experiments performed to demonstrate the regulation of intramembrane proteolysis *in vitro* by exemplary chimeric non-Notch polypeptides described herein.

[0191] In these experiments, the reference receptor was an optimized CD8α Notch receptor (HingeNotch) composed of a truncated CD8α extracellular domain (ECD), a transmembrane domain (TMD) of human Notch1, and a C-terminal juxtamembrane domain (JMD/STS) from Notch1. T cells expressing this anti-CD19 HingeNotch were able to activate a response element in the presence of CD19+ K562 sender cells. This activation was boosted when a co-expressed anti-ALPPL2 CAR is activated, providing a T cell activation stimulus. The results of these experiments are schematically presented in **FIGS. 1A-1C**.

[0192] It was observed that although all receptors expressed at high levels, the otherwise-active Alcadein-gamma (CSTLN2) TMD did not function with its cognate, but inactive, STS/JMD sequence. In particular, by replacing the Notch1 TMD and JMD/STS with the equivalent domains from CLSTN2, it was observed that receptor activity was undetectable. Although the CLSTN2 TMD performed well in prior TMD screening experiments (data not shown), the CLSTN2 JMD/STS was found to be non-functional. It was also observed that by restoring the Notch1 JMD, the receptor activity with the CLSTN2 TMD was restored.

[0193] Remarkably, it was observed that receptor signaling was restored by replacing the CSTLN2 JMD/STS with a more active JMD/STS from KCNE3 (RSRKVDKR; SEQ ID NO: 146) or PTPRF (KRKRTH; SEQ ID NO: 108), *e.g.*, producing a functional receptor when paired with the CLSTN2 TMD. This result indicates that the original CLSTN2 JMD was functionally limiting.

[0194] In summary, the experimental results described in this Example demonstrate that assembly of a non-Notch SynRIPR using the CLSTN2 TMD and JMD results in an inactive receptor, however receptor function was restored when the CLSTN2 JMD was replaced with a higher performing JMD.

[0195] As discussed above, all existing functional SynNotch receptors have included sequence derived from Notch family members. To demonstrate the versatility of the modular receptor assembly approach, the experiments described in this Example have been designed to engineer ligand-activated receptors from the ground up based on receptor components that were completely devoid of Notch sequences. The experimental results described herein illustrate the ability to build new functional synthetic regulated intramembrane proteolysis receptors from a set of functional parts, which in turns demonstrates that synthetic biology approach of receptor assembly is capable of generating receptors that function like Notch receptors but can be rationally customized in their activity.

EXAMPLE 8

Modular assembly of SynRIPRs

[0196] This Example describes experiments performed to illustrate that synthetic receptors can be assembled in a modular fashion by combining a ligand binding domain, an ECD, a TMD, a JMD, and a transcription factor.

[0197] In these experiments, an optimized CD8α Hinge ECD was selected for additional testing due to its robust expression and lack of ligand-independent signaling. In the experiments below, the Notch1 JMD (STS) was kept constant for TMD selection, whereas the Notch1 TMD was kept constant for JMD (STS) selection.

[0198] For selection of TMD, this CD8α Hinge ECD was combined with the anti-CD19 scFV, a variety of high-performing TMDs from previous screening, the Notch1 JMD, and transcriptional regulator Gal4VP64. T cells expressing these receptors were co-incubated with CD19+ sender K562 cells for 48 hours and production of a BFP reporter was measured using flow cytometry. The Notch1 TMD and two TMD mutants were selected due to their low levels of ligand-independent signaling.

[0199] For selection of JMD, the optimized CD8α Hinge ECD was paired with the anti-CD19 scFV, the Notch1 TMD, a variety of JMDs, and transcriptional regulator Gal4VP64. T cells expressing these receptors were co-incubated with CD19+ sender K562 cells and production of a BFP reporter was measured using flow cytometry. The Notch1, NRG1, and Notch2 JMDs were selected due to their variable output production levels allowing for signal tuning.

[0200] In these experiments, T cells expressing high-performing "SynRIPR → BFP expression" circuits were co-incubated with sender cells for 48 hours. BFP output was measured using flow cytometry. The results of these experiments are schematically presented in **FIG. 2**.

[0201] In summary, the experiments described herein illustrate that synthetic regulated intramembrane proteolysis receptor scaffolds suitable for clinical translation can be designed and assembled by choosing an ECD, TMD, and JMD for further testing. Exemplary design criteria included robust expression, high ligand-dependent activation, and low ligand-independent activation under both basal and activated T cell conditions. In one exemplary workflow, one could initially select the optimized CD8α-hinge ECD, due to its strong expression and selective response to ligand, and screened it with a selection of high-performing TMDs and JMDs. As the assembly of SynRIPRs suggests a roughly additive effect for each component to total receptor function, an optimization search could be simplified by screening through TMDs and JMDs with constant Notch1 complementary components. From experimentation, a decision was made to maintain the Notch1 TMD due to its robust activation and best-in-class levels of ligand-independent signaling, along with the ready availability of mutants for tunability. This ECD-TMD combination was screened against a panel of JMDs, choosing a set of SNIPRs (synthetic intramembrane proteolysis receptors) with a range of activation levels. It was observed that although SynRIPR expression levels varied between TMDs and JMDs, these differences did not entirely correlate with receptor activation, which seems to indicate a more pleotropic role for the JMD.

[0202] While particular alternatives of the present disclosure have been disclosed, it is to be understood that various modifications and combinations are possible and are contemplated within the true spirit and scope of the appended claims. There is no intention, therefore, of limitations to the exact abstract and disclosure herein presented.

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CLAIMS

WHAT IS CLAIMED IS:

1. A chimeric polypeptide comprising, from N-terminus to C-terminus:

a) an extracellular binding domain (ECD) having a binding affinity for a selected ligand;

b) a linking sequence;

c) a transmembrane domain(TMD) having at least about 80% sequence identity to the transmembrane domain of a Type 1 transmembrane receptor and comprising one or more ligand-inducible proteolytic cleavage sites; and

d) an intracellular domain (ICD) comprising a transcriptional regulator, wherein binding of the selected ligand to the extracellular binding domain induces cleavage at the ligand-inducible proteolytic cleavage site between the transcriptional regulator and the linking sequence,

and wherein the chimeric polypeptide does not comprise a sequence from a Notch receptor.

2. The chimeric polypeptide of claim 1, further comprising a stop-transfer sequence (STS) positioned between the TMD and the ICD, wherein the STS is heterologous to the TMD.

3. The chimeric polypeptide of any one of claims 1 to 2, wherein the TMD comprises a polypeptide sequence having at least 80% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor and comprises a γ-secretase cleavage site.

4. The chimeric polypeptide of any one of claims 1 to 3, wherein the TMD comprises a polypeptide sequence having at least 90% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor and comprises a γ-secretase cleavage site.

5. The chimeric polypeptide of any one of claims 1 to 4, wherein the TMD comprises a polypeptide sequence having at least 95% sequence identity to a transmembrane domain from a Type 1 transmembrane receptor and comprises a γ-secretase cleavage site.

6. The chimeric polypeptide of any one of claims 1 to 5, wherein the Type 1 transmembrane receptor is selected from the group consisting of CLSTN1, CLSTN2, APLP1,

APLP2, LRP8, APP, BTC, TGBR3, SPN, CD44, CSF1R, CXCL16, CX3CL1, DCC, DLL1, DSG2, DAG1, CDH1, EPCAM, EPHA4, EPHB2, EFNB1, EFNB2, ErbB4, GHR, HLA-A, IFNAR2, IL1R1, IL1R2, IL6R, INSR, ERN1, ERN2, JAG2, KCNE1, KCNE2, KCNE3, KCNE4, KL, CHL1, PTPRF, SCN1B, SCN3B, NPR3, NGFR, PLXDC2, PAM, AGER, ROBO1, SORCS3, SORCS1, SORL1, SORT1, SDC1, SDC2, TYR, TYRP1, DCT, VASN, FLT1, CDH5, PKHD1, NECTIN1, PCDHGC3, NRG1, LRP1B, CDH2, NRG2, PTPRK, SCN2B, Nradd, and PTPRM, and comprises a γ-secretase cleavage site.

7. The chimeric polypeptide of claim 6, wherein the Type 1 transmembrane receptor is APP, CLSTN1, CLSTN2, EPCAM, KCNE3, NECTIN1, PCDHGC3, and PTPRF.

8. The chimeric polypeptide of any one of claims 1 to 7, wherein the STS comprises a sequence having at least 70% sequence identity to a STS sequence from CSF1R, CXCL16, DAG1, GHR, PTPRF, AGER, KL, NRG1, LRP1B, Jag2, EPCAM, KCNE3, CDH2, NRG2, PTPRK, BTC, EPHA3, IL1R2, PTPRF, or PTPRM.

9. The chimeric polypeptide of claim 8, wherein the STS comprises a sequence having at least 70% sequence identity to a STS sequence from CSF1R, DAG1, AGER, NRG1, KCNE3, PTPRF, or PTPRM.

10. The chimeric polypeptide of any one of claims 1 to 9, wherein the extracellular domain comprises an antigen-binding moiety capable of binding to a ligand on the surface of a cell.

11. The chimeric polypeptide of any one of claims 1 to 10, wherein the cell is a pathogenic cell.

12. The chimeric polypeptide of any one of claims 1 to 11, wherein the ligand comprises a protein or a carbohydrate.

13. The chimeric polypeptide of any one of claims 1 to 12, wherein the ligand is selected from the group consisting of CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3d, CD3e, CD3g, CD4, CD5, CD7, CD8a, CD8b, CD19, CD20, CD21, CD22, CD23, CD25, CD27, CD28, CD33, CD34, CD40, CD45, CD48, CD52, CD59, CD66, CD70, CD71, CD72, CD73, CD79A, CD79B, CD80 (B7.1), CD86 (B7.2), CD94, CD95, CD134, CD140 (PDGFR4), CD152, CD154,

CD158, CD178, CD181 (CXCR1), CD182 (CXCR2), CD183 (CXCR3), CD210, CD246, CD252, CD253, CD261, CD262, CD273 (PD-L2), CD274 (PD-L1), CD276 (B7H3), CD279, CD295, CD339 (JAG1), CD340 (HER2), EGFR, FGFR2, CEA, AFP, CA125, MUC-1, and MAGE, Alkaline phosphatase, placental-like 2 (ALPPL2), B-cell maturation antigen (BCMA), Green Fluorescent Protein (GFP), Enhanced Green Fluorescent Protein (EGFP), and Signal regulatory protein α (SIRPα).

14. The chimeric polypeptide of any one of claims 1 to 13, wherein the ligand is selected from cell surface receptors, adhesion proteins, integrins, mucins, lectins, tumor-associated antigens, and tumor-specific antigens.

15. The chimeric polypeptide of any one of claims 1 to 14 wherein the ligand is a tumor-associated antigen or a tumor-specific associated antigen.

16. The chimeric polypeptide of any one of claims 1 to 15, wherein the extracellular binding domain comprises the ligand-binding portion of a receptor.

17. The chimeric polypeptide of any one of claims 10 to 16, wherein the antigen-binding moiety is selected from the group consisting of an antibody, a nanobody, a diabody, a triabody, or a minibody, a $F(ab')_2$ fragment, a Fab fragment, a single chain variable fragment (scFv), a single domain antibody (sdAb), or a functional fragment thereof.

18. The chimeric polypeptide of claim 17, wherein the antigen-binding moiety comprises an scFv.

19. The chimeric polypeptide of any one of claims 10 to 18, wherein the antigen-binding moiety is a tumor-associated antigen selected from the group consisting of CD19, B7H3 (CD276), BCMA (CD269), ALPPL2, CD123, CD171, CD179a, CD20, CD213A2, CD22, CD24, CD246, CD272, CD30, CD33, CD38, CD44v6, CD46, CD71, CD97, CEA, CLDN6, CLECL1, CS-1, EGFR, EGFRvIII, ELF2M, EpCAM, EphA2, Ephrin B2, FAP, FLT3, GD2, GD3, GM3, GPRC5D, HER2 (ERBB2/neu), IGLL1, IL-11Ra, KIT (CD117), MUC1, NCAM, PAP, PDGFR-β, PRSS21, PSCA, PSMA, ROR1, SIRPα, SSEA-4, TAG72, TEM1/CD248, TEM7R, TSHR, VEGFR2, ALPI, citrullinated vimentin, cMet, and Axl.

20. The chimeric polypeptide of claim 19, wherein the tumor-associated antigen is CD19, CEA, HER2, MUC1, CD20, BCMA, ALPPL2, or EGFR.

21. The chimeric polypeptide of claim 20, wherein the tumor-associated antigen is CD19.

22. The chimeric polypeptide of any one of claims 1 to 21, wherein the ligand-inducible proteolytic cleavage site is a γ-secretase cleavage site.

23. The chimeric polypeptide of any one of claims 1 to 22, wherein the transcriptional regulator comprises a transcriptional activator, or a transcriptional repressor.

24. The chimeric polypeptide of any one of claims 1 to 23, wherein the ICD comprises a nuclear localization sequence and a transcriptional regulator sequence selected from Gal4-VP16, Gal4-VP64, tetR-VP64, ZFHD1-VP64, Gal4-KRAB, and HAP1-VP16.

25. The chimeric polypeptide of any one of claims 1 to 24, further comprising a signal sequence, a detectable label, a tumor-specific cleavage site, a disease-specific cleavage site, or a combination thereof.

26. The chimeric polypeptide of any one of claims 2 to 25, wherein the STS comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 85-156 and 173.

27. The chimeric polypeptide of any one of claims 2 to 25, wherein the STS comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 89, 92, 108, 115, 138, 146, and 156.

28. The chimeric polypeptide of any one of claims 1 to 27, wherein the hinge domain is capable of promoting oligomer formation of the chimeric polypeptide via intermolecular disulfide bonding.

29. The chimeric polypeptide of any one of claims 1 to 28, wherein the linking sequence comprises an amino acid sequence having at least 80% sequence identity to a hinge domain derived from CD8α hinge domain, a CD28 hinge domain, a CD152 hinge domain, a PD-1 hinge domain, a CTLA4 hinge domain, an OX40 hinge domain, an IgG1 hinge domain, an IgG2 hinge

domain, an IgG3 hinge domain, and an IgG4 hinge domain, or a functional variant of any thereof.

30. The chimeric polypeptide of claim 29, wherein the hinge domain is derived from a CD8α hinge domain or a functional variant thereof.

31. The chimeric polypeptide of claim 30, wherein the hinge domain comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 157-161.

32. The chimeric polypeptide of any one of claims 1 to 31, wherein the TMD comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 1-84, 178, 182-185, and 190-192.

33. The chimeric polypeptide of claim 32, wherein the TMD comprises an amino acid sequence having at least 90% sequence identity to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64.

34. The chimeric polypeptide of any one of claims 1 to 33, wherein the TMD comprises an amino acid sequence having at least 95% sequence identity to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64.

35. The chimeric polypeptide of claim 34, wherein the TMD comprises an amino acid sequence substantially identical to any one of SEQ ID NOS: 1-2, 6, 20, 43, 39, 54, and 64.

36. The chimeric polypeptide of any one of claims 1 to 35, wherein:

a) the linking sequence comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NOS: 157-161;
b) the TMD comprises an amino acid sequence having at least 80% sequence identity to any one of SEQ ID NO: 1-84, 178, 182-185, and 190-192; and
c) the STS comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 85-156 and 173.

37. A recombinant nucleic acid comprising a nucleotide sequence encoding a chimeric polypeptide according to any one of claims 1 to 36.

38. The recombinant nucleic acid of claim 37, wherein the nucleotide sequence is incorporated into an expression cassette or an expression vector.

39. The recombinant nucleic acid of claim 38, wherein the expression vector is a viral vector.

40. The recombinant nucleic acid of claim 39, wherein the viral vector is a lentiviral vector, an adenovirus vector, an adeno-associated virus vector, or a retroviral vector.

41. The recombinant nucleic acid of claim 40, wherein the viral vector is a lentivival vector.

42. A recombinant cell comprising:

a) a chimeric polypeptide according to any one of claims 1 to 36; and/or

b) a recombinant nucleic acid according to any one of claims 37 to 41.

43. The recombinant cell of claim 42, wherein the cell is a mammalian cell.

44. The recombinant cell of claim 43, wherein the mammalian cell is an immune cell, a neuron, an epithelial cell, an endothelial cell, or a stem cell.

45. The recombinant cell of claim 44, wherein the immune cell is a B cell, a monocyte, a natural killer cell, a basophil, an eosinophil, a neutrophil, a dendritic cell, a macrophage, a regulatory T cell, a helper T cell, a cytotoxic T cell, or other T cell.

46. The recombinant cell of any one of claims 42 to 45, further comprising:

a) a second chimeric polypeptide according to any one of claims 1 to 36; and/or

b) a second nucleic acid according to any one of claims 37 to 41;

wherein the first chimeric polypeptide and the second chimeric polypeptide do not have the same sequence, and/or the first nucleic acid or the second nucleic acid do not have the same sequence.

47. The recombinant cell of claim 46, wherein the chimeric polypeptide modulates the expression and/or activity of the second chimeric polypeptide.

48. The recombinant cell of any one of claims 42 to 47, further comprising an expression cassette encoding a protein of interest operably linked to a promoter, wherein expression of the protein is modulated by the transcriptional regulator encoded by the chimeric receptor.

49. The recombinant cell of claim 48, wherein the protein of interest is heterologous to the cell.

50. The recombinant cell of claim 48 or 49, wherein the promoter is GAL4.

51. The recombinant cell of claim 48 or 50, wherein the protein of interest is a cytokine, a cytotoxin, a chemokine, an immunomodulator, a pro-apoptotic factor, an anti-apoptotic factor, a hormone, a differentiation factor, a de-differentiation factor, an immune cell receptor, or a reporter.

52. A cell culture comprising a recombinant cell according to any one of claims 42 to 51, and a culture medium.

53. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and one or more of the following:

a) a recombinant nucleic acid according to any one of claims 37 to 41; or
b) a recombinant cell according to any one of claims 42 to 51.

54. The pharmaceutical composition of claim 53, wherein the composition comprises a recombinant nucleic acid according to any one of claims 37 to 41, and a pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 54, wherein the recombinant nucleic acid is encapsulated in a viral capsid or a lipid nanoparticle.

56. A method for modulating an activity of a cell, the method comprising:

a) providing a recombinant cell according to any one of claims 42 to 51; and
b) contacting the recombinant cell with the selected ligand, wherein binding of the selected ligand to the extracellular binding domain induces cleavage of a ligand-inducible proteolytic cleavage site and releases the transcriptional regulator, wherein the released transcriptional regulator modulates an activity of the recombinant cell.

57. The method of claim 56, the contacting is carried out *in vivo*, *ex vivo*, or *in vitro*.

58. The method of any one of claims 56 to 57, wherein the activity of the cell is selected from the group consisting of: expression of a selected gene of the cell, proliferation of the cell, apoptosis of the cell, non-apoptotic death of the cell, differentiation of the cell, de-differentiation of the cell, migration of the cell, secretion of a molecule from the cell, cellular adhesion of the cell, and cytolytic activity of the cell.

59. The method of any one of claims 56 to 58, wherein the released transcriptional regulator modulates expression of a gene product of the cell.

60. The method of any one of claims 56 to 59, wherein the released transcriptional regulator modulates expression of a heterologous gene product.

61. The method of any one of claims 59 to 60, wherein the gene product of the cell is selected from the group consisting of a chemokine, a chemokine receptor, a chimeric antigen receptor, a cytokine, a cytokine receptor, a differentiation factor, a growth factor, a growth factor receptor, a hormone, a metabolic enzyme, a pathogen derived protein, a proliferation inducer, a receptor, an RNA guided nuclease, a site-specific nuclease, a T cell receptor, a toxin, a toxin-derived protein, a transcriptional regulator, a transcriptional activator, a transcriptional repressor, a translational regulator, a translational activator, a translational repressor, an activating immuno-receptor, an antibody, an apoptosis inhibitor, an apoptosis inducer, an engineered T cell receptor, an immuno-activator, an immuno-inhibitor, and an inhibiting immuno-receptor.

62. The method of any one of claims 56 to 61, wherein the released transcriptional regulator modulates differentiation of the cell, and wherein the cell is an immune cell, a stem cell, a progenitor cell, or a precursor cell.

63. A method for inhibiting an activity of a target cell in an individual, the method comprising administering to the individual an effective number of the recombinant cell according to any one of claims 42 to 51, wherein the recombinant cell inhibits an activity of the target cell in the individual.

64. The method of claim 63, wherein the target cell is an acute myeloma leukemia cell, an anaplastic lymphoma cell, an astrocytoma cell, a B-cell cancer cell, a breast cancer cell, a colon cancer cell, an ependymoma cell, an esophageal cancer cell, a glioblastoma cell, a glioma cell, a leiomyosarcoma cell, a liposarcoma cell, a liver cancer cell, a lung cancer cell, a mantle cell lymphoma cell, a melanoma cell, a neuroblastoma cell, a non-small cell lung cancer cell, an oligodendroglioma cell, an ovarian cancer cell, a pancreatic cancer cell, a peripheral T-cell lymphoma cell, a renal cancer cell, a sarcoma cell, a stomach cancer cell, a carcinoma cell, a mesothelioma cell, or a sarcoma cell.

65. The method of claim 63, wherein the target cell is a pathogenic cell.

66. A method for the treatment of a disease in an individual in need thereof, the method comprising: administering to the individual a first therapy comprising an effective number of the recombinant cell according to any one of claims 42 to 51, wherein the recombinant cell treats the disease in the individual.

67. The method of claim 66, further comprising administering to the individual a second therapy.

68. The method of claim 67, wherein the second therapy is selected from the group consisting of chemotherapy, radiotherapy, immunotherapy, hormonal therapy, or toxin therapy.

69. The method of any one of claims 66 to 68, wherein the first therapy and the second therapy are administered together, in the same composition or in separate compositions.

70. The method any one of claims 67 to 69, wherein the first therapy and the second therapy are administered simultaneously.

71. The method of any one of claims 67 to 68, wherein the first therapy and the second therapy are administered sequentially.

72. The method of claim 71, wherein the first therapy is administered before the second therapy.

73. The method of claim 71, wherein the first therapy is administered after the second therapy.

74. The method of claim 71, wherein the first therapy and the second therapy are administered in rotation.

75. A system for modulating an activity of a cell, inhibiting a target cancer cell, or treating a disease in an individual in need thereof, wherein the system comprises one or more of the following:

a) a chimeric polypeptide according to any one of claims 1 to 36;
b) a recombinant nucleic acid according to any one of claims 37 to 41;
c) a recombinant cell according to any one of claims 42 to 51; and
d) a pharmaceutical composition according to any one of claims 53 to 55.

76. A method for making the recombinant cell according to any one of claims 42 to 51, comprising:

a) providing a cell capable of protein expression; and
b) contacting the provided cell with a recombinant nucleic acid according to any one of claims 37 to 41.

77. The method of claim 76, wherein the cell is obtained by leukapheresis performed on a sample obtained from a human subject, and the cell is contacted *ex vivo*.

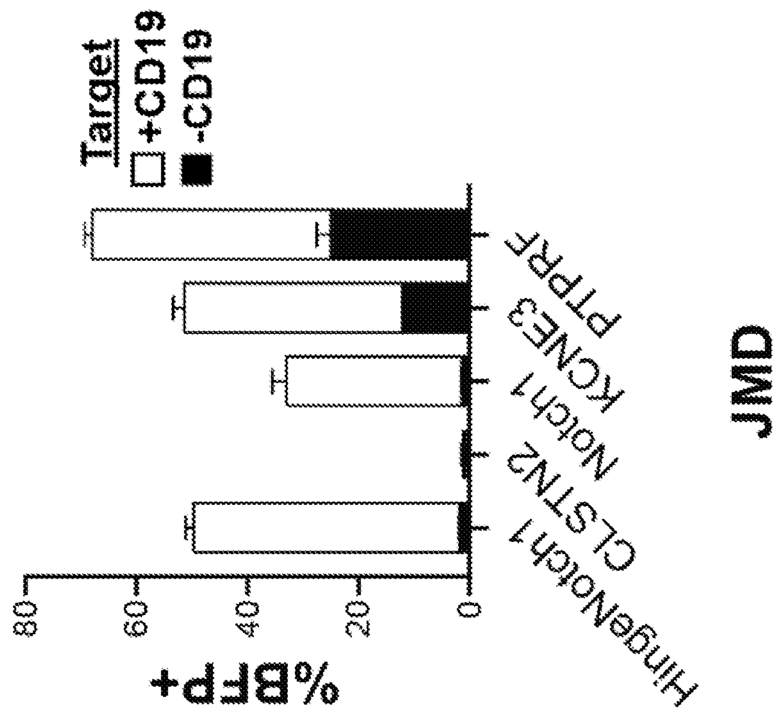
78. The method of claim 76, wherein the recombinant nucleic acid is encapsulated in a viral capsid or a lipid nanoparticle (LNP).

79. The use of one or more of the following for the treatment of a disease:

a) a chimeric polypeptide according to any one of claims 1 to 36;
b) a recombinant nucleic acid according to any one of claims 37 to 41;
c) a recombinant cell according to any one of claims 42 to 51; and
d) a composition according to any one of claims 53 to 55.

80. The use of claim 79, wherein the disease is cancer.

81. The use of the invention of any one of claims 1 to 80, for the manufacture of a medicament for the treatment of a disease.


Target
+CD19
-CD19
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80
60
40
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HingeNotch1
CLSTN2
Notch1
KCNE3
PTPRF
JMD

FIG. 1B

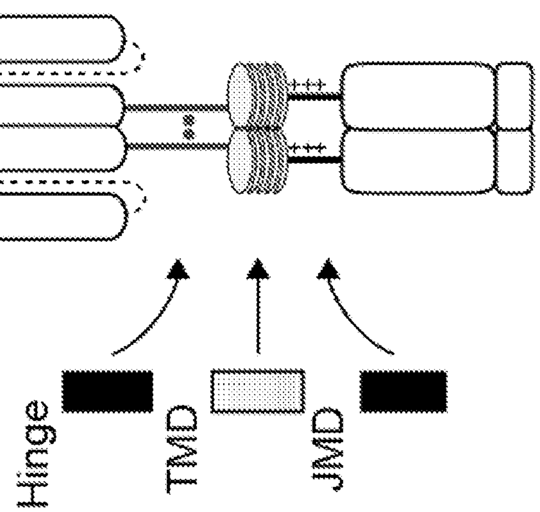
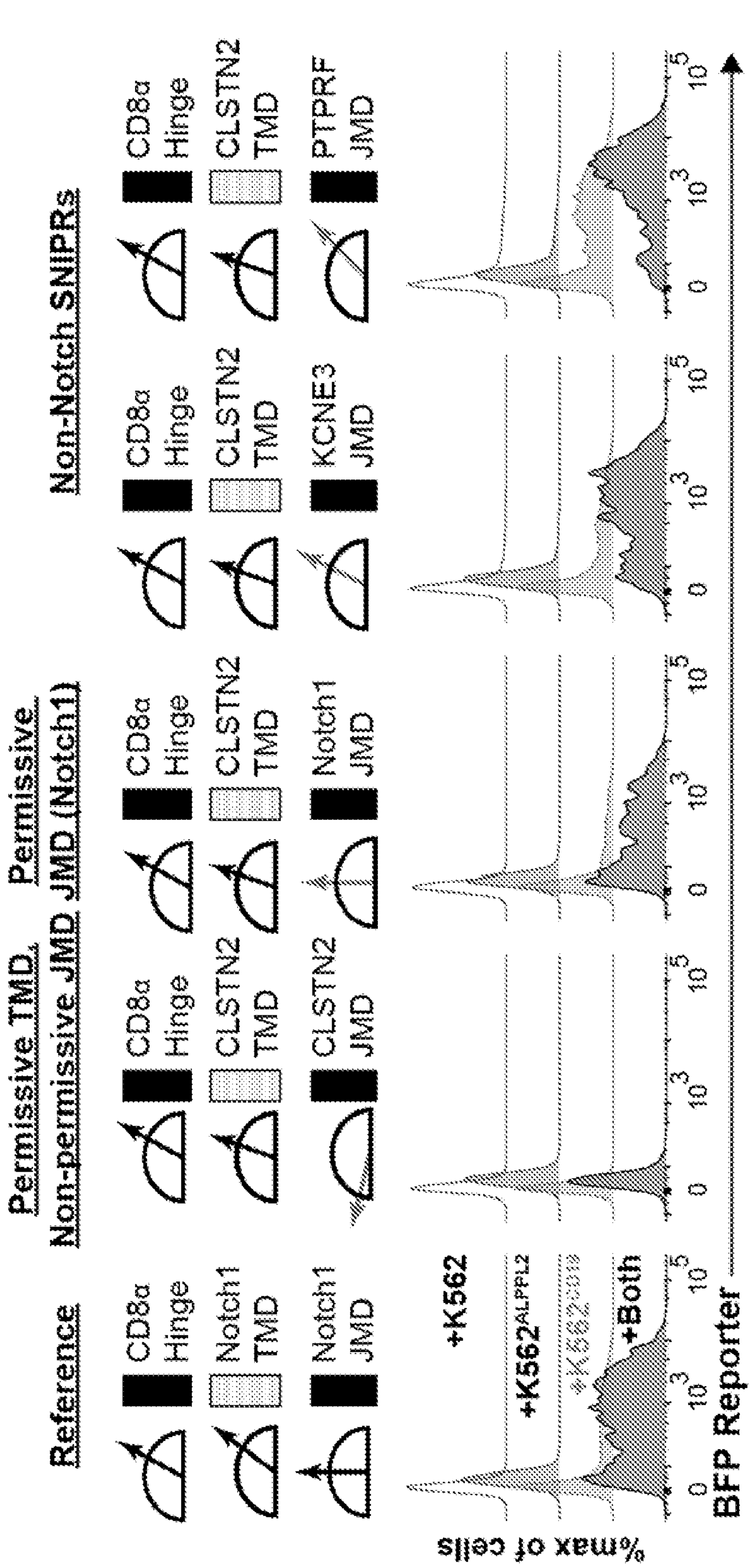

Hinge
TMD
JMD

FIG. 1A


Reference
Permissive TMD,
Non-permissive JMD
Permissive
JMD (Notch1)
Non-Notch SNIPRs
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Hinge
Notch1
TMD
Notch1
JMD
CLSTN2
TMD
CLSTN2
JMD
KCNE3
JMD
PTPRF
JMD
+K562
+K562ALPPL2
+K562CD19
+Both
%max of cells
BFP Reporter
0
10^3
10^5

FIG. 1C

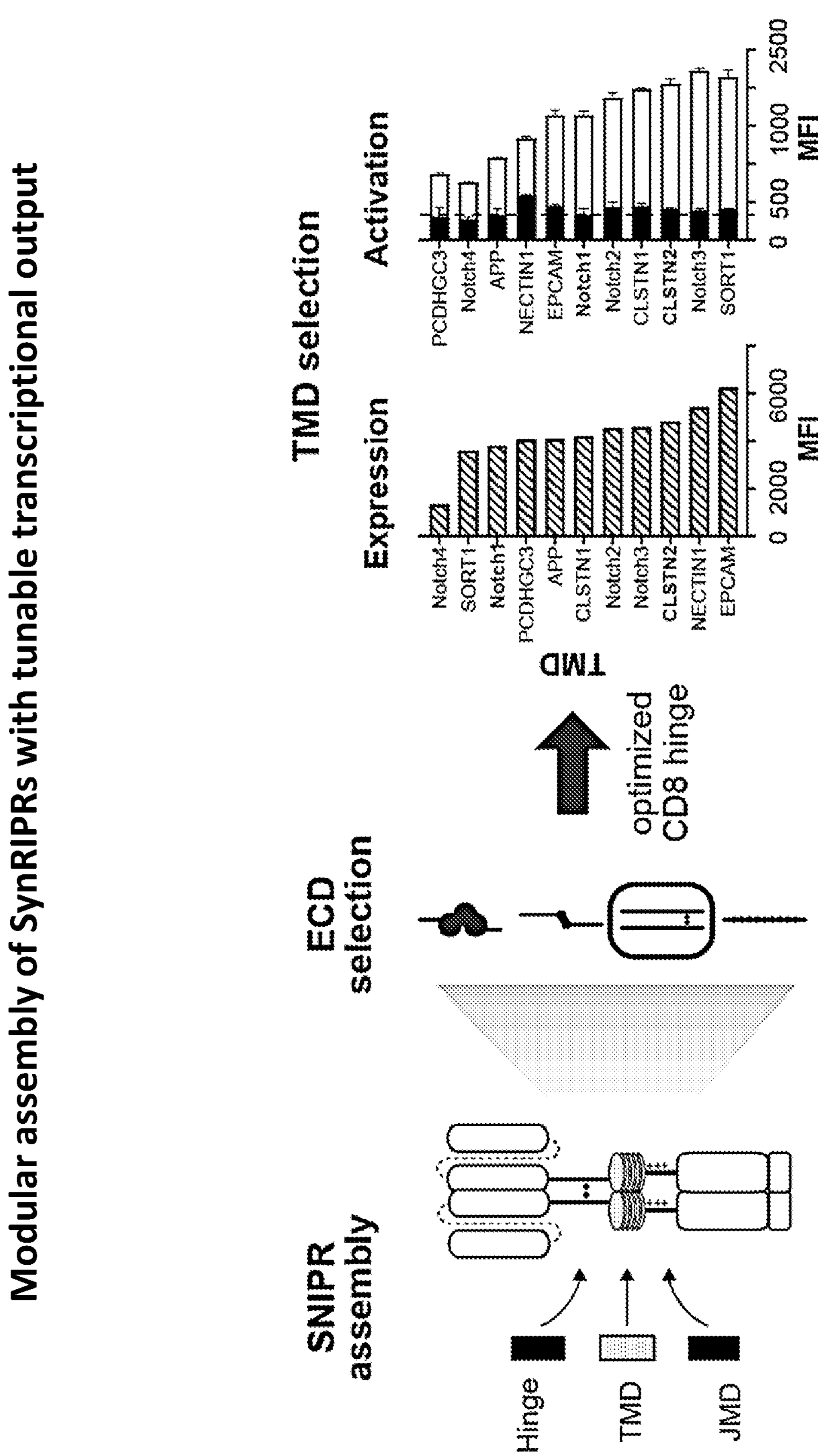
Modular assembly of SynRIPRs with tunable transcriptional output
SNIPR assembly
Hinge
TMD
JMD
ECD selection
optimized CD8 hinge
TMD
TMD selection
Expression
Notch4
SORT1
Notch1
PCDHGC3
APP
CLSTN1
Notch2
Notch3
CLSTN2
NECTIN1
EPCAM
0
2000
6000
MFI
Activation
PCDHGC3
Notch4
APP
NECTIN1
EPCAM
Notch1
Notch2
CLSTN1
CLSTN2
Notch3
SORT1
0
500
1000
2500
MFI

FIG. 2

Modular assembly of SynRIPRs with tunable transcriptional output

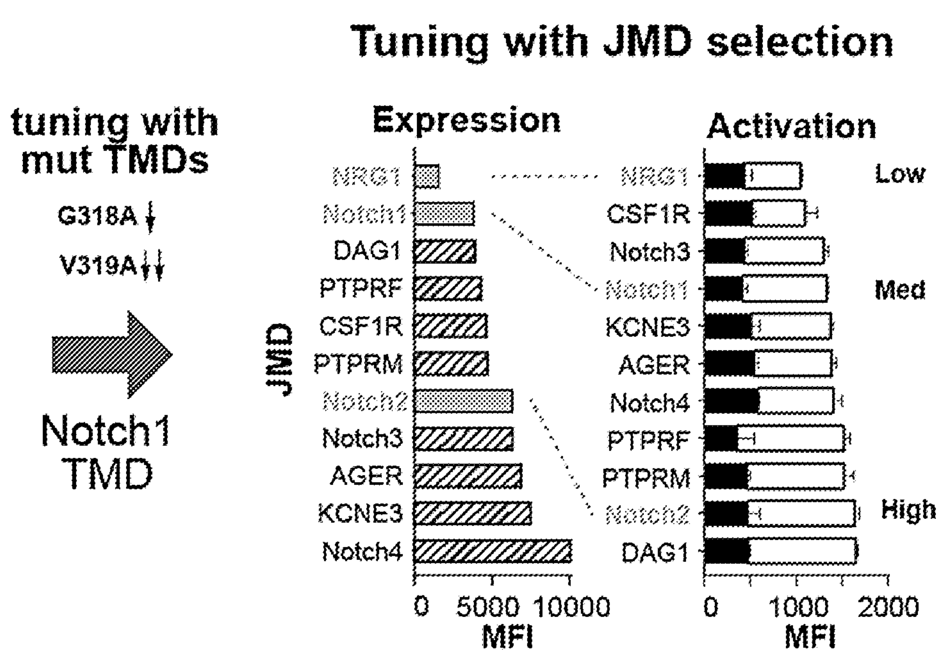

FIG. 2 (Cont.)

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<150> US 63/164,995
<151> 2021-03-23

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Ile Val Ile Ser Leu Val Met Leu
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1   5   10   15

Ile Val Ile Thr Leu Val Met Leu
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Ala Leu Trp Tyr Ile Tyr Ser

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Leu Val Ala Leu Leu Leu Leu Trp
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Val Cys Ile Ala Val Asn Ser
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Leu Leu Leu Leu Tyr
            20

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Val Val Ile Val Ala Val Ile Cys Thr
            20                  25
```

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Cys Ala Ala Val Val Val Cys Val
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```

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Leu Ile Val Gly Ile Cys
            20

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Leu Leu Leu Leu Phe Leu
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Ile Ala Ala Phe Val Ile Ser
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Ile Ile Ile Phe Leu Thr Val Leu Leu Leu
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```

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Gly Leu Thr Phe Ala Val Tyr Val
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            20

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Gly Ser Ile Tyr Leu Phe Leu
            20

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Phe Ile Ile Thr Tyr Pro Leu Ser Met
            20   25

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1               5                   10                  15


Ile Leu Phe Val Met
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```

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1               5                   10                  15


Ala Cys Val Val Leu Cys Val Trp Trp Thr
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Gly Ile Met Leu Ser Tyr Ile
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Thr Val Cys Phe Val
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Ala Ile Leu Leu Phe
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<223> LRP2 TMD

<400> 46

Ala Val Ala Val Leu Leu Thr Ile Leu Leu Ile Val Val Ile Gly Ala
1   5   10   15

Leu Ala Ile Ala Gly Phe Phe
            20

<210> 47
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> LRP6 TMD

<400> 47

Thr Asn Thr Val Gly Ser Val Ile Gly Val Ile Val Thr Ile Phe Val
1   5   10   15

Ser Gly Thr Val Tyr Phe Ile Cys Gln
            20   25

<210> 48
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> MUC1 TMD

<400> 48

```
Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala
1               5                   10                  15

Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys
            20                  25
```

<210> 49
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CDH2 TMD

<400> 49

```
Ile Ile Ala Ile Leu Leu Cys Ile Ile Ile Leu Leu Ile Leu Val Leu
1               5                   10                  15

Met Phe Val Val Trp Met
            20
```

<210> 50
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN1B TMD

<400> 50

Ile Met Met Tyr Val Leu Ile Val Val Leu Thr Ile Trp Leu Val Ala
1   5   10   15

Glu Met Ile Tyr Cys Tyr
            20

<210> 51
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN2B TMD

<400> 51

Val Ile Val Gly Ala Ser Val Gly Gly Phe Leu Ala Val Val Ile Leu
1   5   10   15

Val Leu Met Val Val
            20

<210> 52
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN3B TMD

<400> 52

```
Ile Met Met Tyr Ile Leu Leu Val Phe Leu Thr Leu Trp Leu Leu Ile
1               5                   10                  15


Glu Met Ile Tyr Cys Tyr
            20
```

<210> 53
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN4B TMD

<400> 53

```
Thr Leu Ile Ile Leu Ala Val Val Gly Gly Val Ile Gly Leu Leu Ile
1               5                   10                  15


Leu Ile Leu Leu Ile
            20
```

<210> 54
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NECTIN1 TMD

<400> 54

Ile Ile Gly Gly Val Ala Gly Ser Ile Leu Leu Val Leu Ile Val Val
1   5   10   15

Gly Gly Ile Val Val Ala Leu
            20

<210> 55
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NRG1 TMD

<400> 55

Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val Gly Ile
1   5   10   15

Met Cys Val Val Ala Tyr Cys
            20

<210> 56
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NRG2 TMD

<400> 56

Val Leu Thr Ile Thr Gly Ile Cys Val Ala Leu Leu Val Val Gly Ile

1   5   10   15

Val Cys Val Val Ala Tyr Cys
            20

<210> 57
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NPR3 TMD

<400> 57

Ser Ala Val Thr Gly Ile Val Val Gly Ala Leu Leu Gly Ala Gly Leu
1   5   10   15

Leu Met Ala Phe Tyr Phe Phe
            20

<210> 58
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Nradd TMD

<400> 58

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

Leu Ala Tyr Val Ala Phe

20

<210> 59
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NGFR TMD

<400> 59

```
Leu Ile Pro Val Tyr Cys Ser Ile Leu Ala Ala Val Val Val Gly Leu
1               5                   10                  15


Val Ala Tyr Ile Ala Phe
            20
```

<210> 60
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PAM TMD

<400> 60

```
Val Pro Val Val Leu Ile Thr Thr Leu Leu Val Ile Pro Val Val Val
1               5                   10                  15


Leu Leu Ala Ile Ala Ile Phe Ile
            20
```

<210> 61

<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PLXDC2 TMD

<400> 61

Gly Leu Ile Ile Gly Ile Leu Ile Leu Val Leu Ile Val Ala Thr Ala
1   5   10   15

Ile Leu Val Thr Val Tyr Met Tyr
            20

<210> 62
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PKHD1 TMD

<400> 62

Ile Ile Leu Ala Ala Ser Leu Ser Ser Val Ala Ser Trp Leu Ala Leu
1   5   10   15

Ser Cys Leu Val Cys Cys Trp Leu
            20

<210> 63
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PCDHA4 TMD

<400> 63

```
Val Tyr Leu Ile Ile Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu
1               5                   10                  15

Thr Leu Leu Leu Tyr Thr Ala Leu
            20
```

<210> 64
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PCDHGC3 TMD

<400> 64

```
Leu Leu Leu Ser Leu Ile Leu Val Ser Val Gly Phe Val Val Thr Val
1               5                   10                  15

Phe Gly Val Ile Ile Phe
            20
```

<210> 65
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRZ1 TMD

<400> 65

```
Ala Val Ile Pro Leu Val Ile Val Ser Ala Leu Thr Phe Ile Cys Leu
1               5                   10                  15


Val Val Leu Val Gly Ile Leu Ile Tyr Trp
            20                  25
```

<210> 66
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> AGER TMD

<400> 66

```
Leu Ala Leu Gly Ile Leu Gly Gly Leu Gly Thr Ala Ala Leu Leu Ile
1               5                   10                  15


Gly Val Ile Leu Trp Gln
            20
```

<210> 67
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRK TMD

<400> 67

Ile Ala Gly Ile Ser Ala Gly Ile Leu Val Phe Ile Leu Leu Leu Leu
1   5   10   15

Val Val Ile Leu Ile Val
            20

<210> 68
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRM TMD

<400> 68

Ile Ala Gly Val Ile Ala Gly Ile Leu Leu Phe Val Ile Ile Phe Leu
1   5   10   15

Gly Val Val Leu Val Met
            20

<210> 69
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> ROBO1 TMD

<400> 69

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

Phe Ser Ile Trp Leu Tyr
            20

<210> 70
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORCS3 TMD

<400> 70

Ala Met Leu Met Leu Leu Ser Val Val Phe Val Gly Leu Ala Val Phe
1   5   10   15

Leu Ile Tyr Lys Phe
            20

<210> 71
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORCS1 TMD

<400> 71

Gly Ser Ala Met Leu Met Leu Leu Ser Val Val Phe Val Gly Leu Ala
1   5   10   15

Val Phe Val Ile Tyr
            20

<210> 72
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORL1 TMD

<400> 72

```
Ala Val Val Val Pro Ile Leu Phe Leu Ile Leu Leu Ser Leu Gly Val
1               5                   10                  15

Gly Phe Ala Ile Leu Tyr Thr
            20
```

<210> 73
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORT1 TMD

<400> 73

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

Val Ala Gly Val Leu Ile Val
            20
```

<210> 74
<211> 22

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SDC1 TMD

<400> 74

```
Gly Val Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu
1               5                   10                  15


Val Gly Phe Met Leu Tyr
            20
```

<210> 75
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SDC2 TMD

<400> 75

```
Val Leu Ala Ala Val Ile Ala Gly Gly Val Ile Gly Phe Leu Phe Ala
1               5                   10                  15


Ile Phe Leu Ile Leu Leu Leu Val Tyr
            20                  25
```

<210> 76
<211> 22
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SDC3 TMD

<400> 76

```
Ala Val Ile Val Gly Gly Val Val Gly Ala Leu Phe Ala Ala Phe Leu
1               5                   10                  15

Val Thr Leu Leu Ile Tyr
            20
```

<210> 77
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> TIE1 TMD

<400> 77

```
Gln Leu Ile Leu Ala Val Val Gly Ser Val Ser Ala Thr Cys Leu Thr
1               5                   10                  15

Ile Leu Ala Ala Leu Leu Thr Leu Val Cys Ile
            20                  25
```

<210> 78
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>

<221> MISC_FEATURE
<223> TYR TMD

<400> 78

Trp Leu Leu Gly Ala Ala Met Val Gly Ala Val Leu Thr Ala Leu Leu
1   5   10   15

Ala Gly Leu Val Ser Leu Leu Cys
            20

<210> 79
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> TYRP1 TMD

<400> 79

Ile Ile Ala Ile Ala Val Val Gly Ala Leu Leu Leu Val Ala Leu Ile
1   5   10   15

Phe Gly Thr Ala Ser Tyr Leu Ile
            20

<210> 80
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DCT TMD

<400> 80

Leu Leu Val Val Met Gly Thr Leu Val Ala Leu Val Gly Leu Phe Val
1   5   10   15

Leu Leu Ala Phe Leu Gln Tyr
            20

<210> 81
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> VASN TMD

<400> 81

Leu Leu Ile Ala Pro Ala Leu Ala Ala Val Leu Leu Ala Ala Leu Ala
1   5   10   15

Ala Val Gly Ala Ala Tyr Cys Val
            20

<210> 82
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CDH5 TMD

<400> 82

Ala Val Val Ala Ile Leu Leu Cys Ile Leu Thr Ile Thr Val Ile Thr
1   5   10   15

Leu Leu Ile Phe Leu
20

<210> 83
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> FLT1 TMD

<400> 83

Leu Ile Thr Leu Thr Cys Thr Cys Val Ala Ala Thr Leu Phe Trp Leu
1 5 10 15

Leu Leu Thr Leu Phe Ile
20

<210> 84
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> VLDLR TMD

<400> 84

Ala Ala Trp Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala Val
1 5 10 15

Gly Gly Tyr Leu Met Trp
20

<210> 85
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> APLP1 STS

<400> 85

Arg Arg Lys Lys
1

<210> 86
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> APLP2 STS

<400> 86

Arg Lys Arg
1

<210> 87
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE

<223> APP STS

<400> 87

Lys Lys Lys
1

<210> 88
<211> 1
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> TGBR3 STS

<400> 88

His
1

<210> 89
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CSF1R STS

<400> 89

Lys Tyr Lys Gln Lys Pro Lys
1   5

<210> 90
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CXCL16 STS

<400> 90

Lys Arg Arg Arg
1

<210> 91
<211> 2
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CX3CL1 STS

<400> 91

Arg Lys
1

<210> 92
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DAG1 STS

<400> 92

Arg Lys Lys Arg Lys Gly Lys

1   5

<210> 93
<211> 2
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DCC STS

<400> 93

Arg Arg
1

<210> 94
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DNER STS

<400> 94

Arg Ile Ser Arg
1

<210> 95
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DSG2 STS

<400> 95

Lys Cys Gly Lys Gly Ala Lys
1   5

<210> 96
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CDH1 STS

<400> 96

Arg Arg Arg
1

<210> 97
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> GHR STS

<400> 97

Lys Gln Gln Arg Ile Lys
1   5

<210> 98
<211> 3

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> HLA-A STS

<400> 98

Arg Arg Lys
1

<210> 99
<211> 1
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> IFNAR2 STS

<400> 99

Lys
1

<210> 100
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> IGF1R STS

<400> 100

His Arg Lys Arg
1

<210> 101
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> IL1R1 STS

<400> 101

Lys Ile Phe Lys
1

<210> 102
<211> 1
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> ERN2 STS

<400> 102

Arg
1

<210> 103
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> KCNE1 STS

<400> 103

Arg Ser Lys Lys Leu Glu His
1   5

<210> 104
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> KCNE2 STS

<400> 104

Lys Ser Lys Arg Arg Glu His
1   5

<210> 105
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CHL1 STS

<400> 105

Lys Arg Asn Arg Gly Gly Lys
1   5

<210> 106
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> LRP1 STS

<400> 106

Lys Arg Arg
1

<210> 107
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> LRP2 STS

<400> 107

His Tyr Arg Arg
1

<210> 108
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRF STS

<400> 108

Lys Arg Lys Arg Thr His
1   5

<210> 109
<211> 2
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN1B STS

<400> 109

Lys Lys
1

<210> 110
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN3B STS

<400> 110

Arg Lys Val Ser Lys
1   5

<210> 111
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NPR3 STS

<400> 111

Arg Lys Lys Tyr Arg
1   5

<210> 112
<211> 2
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NGFR STS

<400> 112

Lys Arg
1

<210> 113
<211> 2
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PLXDC2 STS

<400> 113

His His
1

<210> 114
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PAM STS

<400> 114

Arg Trp Lys Lys Ser Arg
1   5

<210> 115
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> AGER STS

<400> 115

Arg Arg Gln Arg Arg
1   5

<210> 116
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>

<221> MISC_FEATURE
<223> ROBO1 STS

<400> 116

Arg His Arg Lys Lys Arg
1   5

<210> 117
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORCS3 STS

<400> 117

Lys Arg Lys
1

<210> 118
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORCS1 STS

<400> 118

Lys Phe Lys Arg Arg
1   5

<210> 119
<211> 4
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SORL1 STS

<400> 119

Lys His Arg Arg
1

<210> 120
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SDC1 STS

<400> 120

Arg Met Lys Lys Lys
1   5

<210> 121
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SDC2 STS

<400> 121

Arg Met Arg Lys Lys
1   5

<210> 122
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SPN STS

<400> 122

Arg Arg Arg Gln Lys Arg Arg
1   5

<210> 123
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> TYR STS

<400> 123

Arg His Lys Arg Lys
1   5

<210> 124
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> TYRP1 STS

<400> 124

Arg Ala Arg Arg
1

<210> 125
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> DCT STS

<400> 125

Arg Arg Leu Arg Lys
1   5

<210> 126
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> VASN STS

<400> 126

Arg Arg Gly Arg
1

<210> 127

<211> 5
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> MISC_FEATURE
<223> FLT1 STS

<400> 127

Arg Lys Met Lys Arg
1   5

<210> 128
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CDH5 STS

<400> 128

Arg Arg Arg Leu Arg Lys Gln Ala Arg Ala His Gly Lys
1   5   10

<210> 129
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PKHD1 STS

<400> 129

Lys Arg Ser Lys Ser Arg Lys Thr Lys
1   5

<210> 130
<211> 8
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> MISC_FEATURE
<223> NECTIN1 STS

<400> 130

Arg Arg Arg Arg His Thr Phe Lys
1   5

<210> 131
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> KL STS

<400> 131

Lys Lys Gly Arg Arg Ser Tyr Lys
1   5

<210> 132
<211> 15
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> IL6R STS

<400> 132

Arg Phe Lys Lys Thr Trp Lys Leu Arg Ala Leu Lys Glu Gly Lys
1   5   10   15

<210> 133
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> EFNB1 STS

<400> 133

Lys Leu Arg Lys Arg His Arg Lys His
1   5

<210> 134
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CD44 STS

<400> 134

Arg Arg Arg Cys Gly Gln Lys Lys Lys
1   5

<210> 135
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CLSTN1 STS

<400> 135

Arg Ile Arg Ala Ala His Arg Arg Thr Met Arg
1   5   10

<210> 136
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> LRP8 STS

<400> 136

Arg Asn Trp Lys Arg Lys Asn Thr Lys
1   5

<210> 137
<211> 9
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> MISC_FEATURE

<223> PCDHGC3 STS

<400> 137

Lys Val Tyr Lys Trp Lys Gln Ser Arg
1   5

<210> 138
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NRG1 STS

<400> 138

Lys Thr Lys Lys Gln Arg Lys Lys Leu His Asp Arg Leu Arg
1   5   10

<210> 139
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> LRP1B STS

<400> 139

Lys Arg Lys Arg Arg Thr Lys Thr Ile Arg Arg
1   5   10

<210> 140
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
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<223> JAG2 STS

<400> 140

Arg Lys Arg Arg Lys Glu Arg Glu Arg Ser Arg Leu Pro Arg
1   5   10

<210> 141
<211> 9
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> EFNB2 STS

<400> 141

Lys Tyr Arg Arg Arg His Arg Lys His
1   5

<210> 142
<211> 8
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> DLL1 STS

<400> 142

Arg Leu Arg Leu Gln Lys His Arg

1 5

<210> 143
<211> 8
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> CLSTN2 STS

<400> 143

Arg Val Arg Ile Ala His Gln His
1 5

<210> 144
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<223> EPCAM STS

<400> 144

Arg Lys Lys Arg Met Ala Lys Tyr Glu Lys
1 5 10

<210> 145
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> ErbB4 STS

<400> 145

Arg Arg Lys Ser Ile Lys Lys Lys Arg Ala Leu Arg Arg
1   5   10

<210> 146
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> KCNE3 STS

<400> 146

Arg Ser Arg Lys Val Asp Lys Arg
1   5

<210> 147
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CDH2 STS

<400> 147

Lys Arg Arg Asp Lys Glu Arg Gln Ala Lys
1   5   10

<210> 148
<211> 14

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> NRG2 STS

<400> 148

Lys Thr Lys Lys Gln Arg Lys Gln Met His Asn His Leu Arg
1   5   10

<210> 149
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRK STS

<400> 149

Lys Lys Ser Lys Leu Ala Lys Lys Arg Lys
1   5   10

<210> 150
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> BTC STS

<400> 150

His Pro Leu Arg Lys Arg Arg Lys Arg Lys Lys Lys
1   5   10

<210> 151
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> EPHA4 STS

<400> 151

Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys
1   5   10

<210> 152
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> IL1R2 STS

<400> 152

His Arg Arg Cys Lys His Arg Thr Gly Lys
1   5   10

<210> 153
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> KCNE4 STS

<400> 153

Lys Ser Lys Arg Arg Glu Lys Lys
1   5

<210> 154
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> SCN2B STS

<400> 154

Lys Cys Val Arg Arg Lys Lys Glu Gln Lys
1   5   10

<210> 155
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Nradd STS

<400> 155

Lys Cys Trp Arg Ser His Lys Gln Arg
1   5

<210> 156
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> PTPRM STS

<400> 156

Lys Lys Arg Lys Leu Ala Lys Lys Arg Lys
1   5   10

<210> 157
<211> 45
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CD8a hinge

<400> 157

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> 158
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> truncated CD8a hinge

<400> 158

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
            20   25

<210> 159
<211> 39
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> hinge domain

<400> 159

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> 160
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> hinge domain

<400> 160

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
1   5   10   15

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
            20   25

<210> 161
<211> 186
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> hinge domain

<400> 161

Leu His Cys Val Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His
1   5   10   15

Glu Cys Arg Pro Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln
            20   25   30

Asn Thr Val Cys Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val
        35   40   45

Ser Ser Lys Pro Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly
    50   55   60

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

Cys Arg Ala Gly Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp
85 90 95

Cys Ala Pro Cys Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala
100 105 110

Cys Lys Pro Trp Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln
115 120 125

Pro Ala Ser Asn Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro
130 135 140

Ala Thr Gln Pro Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr
145 150 155 160

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

Arg Pro Val Glu Val Pro Gly Gly Arg Ala
180 185

<210> 162
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CD8alpha signal peptide

<400> 162

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>  163
<211>  10
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic construct


<220>
<221>  MISC_FEATURE
<223>  myc-tag

<400>  163

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
1               5                   10


<210>  164
<211>  20
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic construct


<220>
<221>  MISC_FEATURE
<223>  GAL4 DBD recognition motif

<400>  164

Gly Gly Ala Gly Cys Ala Cys Thr Gly Thr Cys Cys Thr Cys Cys Gly
1               5                   10                  15


Ala Ala Cys Gly
            20


<210>  165
<211>  4
<212>  PRT
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<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Exemplary cleavage sequence of MMP-9

<220>
<221> MISC_FEATURE
<222> (2)..(3)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Leu, Ile, Val, Phe, Trp, Tyr, Val, Met, or Pro

<400> 165

Pro Xaa Xaa Xaa
1

<210> 166
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Exemplary cleavage sequence of MMP-9

<220>
<221> MISC_FEATURE
<222> (2)..(4)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Ser or Thr

<400> 166

Pro Xaa Xaa Xaa Xaa
1   5

<210> 167
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Exemplary cleavage sequence of MMP-9

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Leu or Gln

<400> 167

Pro Xaa Gly Met Thr Ser
1   5

<210> 168
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Exemplary cleavage sequence of MMP-9

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Leu or Gln

<400> 168

Pro Xaa Gly Met Thr

1   5

<210> 169
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> exemplary urokinase-type plasminogen activator (uPA) or tissue plasminogen activator (tPA) cleavage site

<400> 169

Val Gly Arg
1

<210> 170
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> exemplary tobacco etch virus (TEV) protease cleavage site

<400> 170

Glu Asn Leu Tyr Thr Gln Ser
1   5

<210> 171
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> exemplary enterokinase cleavage site

<400> 171

Asp Asp Asp Asp Lys
1   5

<210> 172
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> exemplary thrombin cleavage site

<400> 172

Leu Val Pro Arg
1

<210> 173
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Wild-type Notch1 TMD

<400> 173

Phe Met Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly
1   5   10   15

Cys Gly Val Leu Leu Ser

20

<210> 174
<211> 273
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> ECD

<400> 174

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser

<210> 175
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>

<221> MISC_FEATURE
<223> IgG4 N-JMD

<400> 175

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1   5   10

<210> 176
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated Notch1_GIVVLLSmut TMD (a site from EPCAM/NECTIN1 that maintains cleavage (GIVV) was added)

<400> 176

Phe Met Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly
1   5   10   15

Cys Gly Ile Val Val Leu Leu Ser
            20

<210> 177
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated Notch1_GIVVSmut TMD (a site from EPCAM/NECTIN1 that maintains cleavage (GIVV) was added)

<400> 177

Phe Met Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly

1 5 10 15

Cys Gly Ile Val Val Ser
20

<210> 178
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> APP TMD

<400> 178

Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala Thr Val
1 5 10 15

Ile Val Ile Thr Gly Val Met Leu
20

<210> 179
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch2 TMD

<400> 179

Leu Leu Tyr Leu Leu Ala Val Ala Val Val Ile Ile Leu Phe Ile Ile
1 5 10 15

Leu Leu Gly Val Ile Met Ala

20

<210> 180
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch3 TMD

<400> 180

Leu Pro Leu Leu Val Ala Gly Ala Val Leu Leu Leu Val Ile Leu Val
1   5   10   15

Leu Gly Val Met Val Ala
            20

<210> 181
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch3 TMD

<400> 181

Pro Val Leu Cys Ser Pro Val Ala Gly Val Ile Leu Leu Ala Leu Gly
1   5   10   15

Ala Leu Leu Val Leu Gln Leu Ile
            20

<210> 182

<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated AGER _GVLVSmut TMD (the last 4 amino acids of the wild-type AGER TMD were replaced with "LVS" to functionalize the TMD)

<400> 182

Leu Ala Leu Gly Ile Leu Gly Gly Leu Gly Thr Ala Ala Leu Leu Ile
1   5   10   15

Gly Val Leu Val Ser
            20

<210> 183
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated AGER _LLmut TMD (the last 4 amino acids of the wild-type AGER TMD were replaced with "LVS" to functionalize the TMD)

<400> 183

Leu Ala Leu Gly Ile Leu Gly Gly Leu Leu Leu Ala Ala Leu Leu Ile
1   5   10   15

Gly Val Ile Leu Trp Gln
            20

<210> 184
<211> 23
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated ROBO1 TMD (the last 4 amino acids of the wild-type Robo1 TMD were replaced with "GVLLS" to functionalize the TMD

<400> 184

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

Phe Ser Gly Val Leu Leu Ser
            20

<210> 185
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch1 D. rerio TMD

<400> 185

Met Tyr Pro Met Phe Leu Val Leu Leu Ala Leu Ala Val Leu Ala Leu
1   5   10   15

Ala Ala Val Gly Val Val Val Ser
            20

<210> 186
<211> 22
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch1 D. melanogaster TMD

<400> 186

Val Ile Thr Gly Ile Ile Leu Val Ile Ile Ala Leu Ala Phe Phe Gly
1   5   10   15

Met Val Leu Ser Thr Gln
            20

<210> 187
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch1 X. laevis TMD

<400> 187

Pro Met Leu Ser Met Leu Val Ile Pro Leu Leu Ile Ile Phe Val Phe
1   5   10   15

Met Met Val Ile Val Asn
            20

<210> 188
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>

<221> MISC_FEATURE
<223> Notch1 G. gallus TMD

<400> 188

Pro Met Tyr Val Val Val Ala Ala Leu Val Leu Leu Ala Phe Ile Gly
1   5   10   15

Val Gly Val Leu Val Ser
            20

<210> 189
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch1 M. muculs TMD

<400> 189

Leu Met Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly
1   5   10   15

Cys Gly Val Leu Leu Ser
            20

<210> 190
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> CD8a TMD

<400> 190

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> 191
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated CD8a TMD

<400> 191

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 Gly Val Leu Leu Ser
            20   25

<210> 192
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> mutated CD8a TMD

<400> 192

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

Ser Leu Gly Val Leu Val Ser
            20

<210> 193
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch1 STS

<400> 193

Arg Lys Arg Arg Arg
1   5

<210> 194
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch3 STS

<400> 194

Arg Arg Lys Arg Glu His
1   5

<210> 195
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Notch4 STS

<400> 195

```
Arg Arg Arg Arg Glu His
1               5
```

<210> 196
<211> 211
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> Gal4-VP64

<400> 196

```
Met Lys Leu Leu Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu
1               5                   10                  15


Lys Lys Leu Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu
            20                  25                  30


Lys Asn Asn Trp Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro
        35                  40                  45


Leu Thr Arg Ala His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu
    50                  55                  60


Glu Gln Leu Phe Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile
65                  70                  75                  80


Leu Lys Met Asp Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu
                85                  90                  95
```

Phe Val Gln Asp Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala
            100   105   110

Ser Val Glu Thr Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser
        115   120   125

Ala Thr Ser Ser Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu
    130   135   140

Thr Val Ser Ala Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
145   150   155   160

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp
                165   170   175

Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp
            180   185   190

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
        195   200   205

Leu Gly Ser
    210

<210> 197
<211> 558
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ343GIVV

<400> 197

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Phe Met
305   310   315   320

Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly
                325   330   335

Ile Val Val Leu Leu Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser
            340   345   350

Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys
        355   360   365

Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu
    370   375   380

Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His
385   390   395   400

Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu
                405   410   415

Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser
            420   425   430

Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn
        435   440   445

Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp
    450   455   460

Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser
465   470   475   480

Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala
                485   490   495

Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe
            500   505   510

Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
        515   520   525

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
    530   535   540

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
545   550   555

<210> 198
<211> 556
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ343GIVVa

<400> 198

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190
```

```
Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Phe Met
305                 310                 315                 320

Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly
                325                 330                 335

Ile Val Val Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
            340                 345                 350

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
        355                 360                 365

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
    370                 375                 380

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
```

385 390 395 400

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
405 410 415

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
420 425 430

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
435 440 445

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
450 455 460

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
465 470 475 480

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
485 490 495

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
500 505 510

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
515 520 525

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
530 535 540

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
545 550 555

<210> 199
<211> 523
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ373

<400> 199

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Phe Met Tyr
275 280 285

Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val
290 295 300

Leu Leu Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
305 310 315 320

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
325 330 335

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
340 345 350

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
355 360 365

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
    370   375   380

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
385   390   395   400

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
                405   410   415

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
            420   425   430

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
        435   440   445

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
    450   455   460

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
465   470   475   480

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
                485   490   495

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
            500   505   510

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
        515   520

<210> 200
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>

<221> MISC_FEATURE
<223> pIZ377

<400> 200

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
```

180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ile Ala Thr Val
290 295 300

Val Ile Ile Ile Ser Val Cys Met Leu Val Phe Val Val Ala Met Gly
305 310 315 320

Val Tyr Lys Arg Lys Arg Thr His Met Lys Leu Leu Ser Ser Ile Glu
325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
340 345 350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
355 360 365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
370 375 380

```
Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385                 390                 395                 400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
                405                 410                 415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
            420                 425                 430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
        435                 440                 445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
    450                 455                 460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465                 470                 475                 480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
                485                 490                 495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
            500                 505                 510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
        515                 520                 525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530                 535
```

<210> 201
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ378

<400> 201

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

```
Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ile Ala Thr Val
    290                 295                 300

Val Ile Ile Ile Ser Val Cys Met Leu Val Phe Val Val Ala Met Gly
305                 310                 315                 320

Val Tyr Arg Arg Gln Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325                 330                 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340                 345                 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355                 360                 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370                 375                 380
```

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 202
<211> 541
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ379

<400> 202

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175
```

```
Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ile Ala Thr Val
    290                 295                 300

Val Ile Ile Ile Ser Val Cys Met Leu Val Phe Val Val Ala Met Gly
305                 310                 315                 320

Val Tyr Arg Ser Arg Lys Val Asp Lys Arg Met Lys Leu Leu Ser Ser
                325                 330                 335

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
            340                 345                 350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
        355                 360                 365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
```

370 375 380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385 390 395 400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
405 410 415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
420 425 430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
435 440 445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
450 455 460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465 470 475 480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
485 490 495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
500 505 510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
515 520 525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535 540

<210> 203
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD206

<400> 203

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


His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30


Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45


Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60


Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80


His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95


Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110


Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125


Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160


Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175
```

```
Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Gly Ala Ile Ile
    290                 295                 300

Gly Leu Met Val Gly Gly Val Val Ile Ala Thr Val Ile Val Ile Thr
305                 310                 315                 320

Leu Val Met Leu Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
                325                 330                 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
            340                 345                 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
        355                 360                 365
```

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 204
<211> 540
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD206GV

<400> 204

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr

165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Gly Ala Ile Ile
290 295 300

Gly Leu Met Val Gly Gly Val Val Ile Ala Thr Val Ile Val Ile Thr
305 310 315 320

Gly Val Met Leu Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 205
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD207

<400> 205

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160
```

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ile Leu Val Ile
290 295 300

Cys Leu Ile Ala Val Met Val Val Phe Ile Ile Leu Val Ile Gly Val
305 310 315 320

Cys Thr Cys Cys Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 206
<211> 544
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD213

<400> 206

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160
```

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ala Val Gly Leu
290 295 300

Leu Ala Phe Leu Gly Leu Leu Phe Cys Leu Gly Val Ala Met Phe Thr
305 310 315 320

Tyr Gln Ser Leu Gln Gly Cys Pro Arg Lys Arg Arg Arg Met Lys Leu
325 330 335

Leu Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu
340 345 350

Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn

355   360   365

Trp Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg
    370   375   380

Ala His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu
385   390   395   400

Phe Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met
                405   410   415

Asp Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln
            420   425   430

Asp Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu
        435   440   445

Thr Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser
    450   455   460

Ser Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser
465   470   475   480

Ala Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp
                485   490   495

Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp
            500   505   510

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
        515   520   525

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 207
<211> 541
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD214

<400> 207

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160
```

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Leu Leu Val Ile
    290   295   300

Ile Val Val Thr Val Gly Val Ile Thr Val Leu Val Val Val Ile Val
305   310   315   320

Ala Val Ile Cys Thr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser
                325   330   335

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
            340   345   350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
        355   360   365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
    370   375   380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385   390   395   400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
                405   410   415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
            420   425   430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
        435   440   445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
    450   455   460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465   470   475   480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
                485   490   495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
            500   505   510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
        515   520   525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 208
<211> 540

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD215

<400> 208

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


His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30


Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45


Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60


Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80


His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95


Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110


Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125


Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
```

145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Val Ala Val Cys
290 295 300

Ala Gly Val Ile Leu Val Leu Met Leu Leu Leu Gly Cys Ala Ala Val
305 310 315 320

Val Val Cys Val Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
370 375 380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385 390 395 400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
405 410 415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
420 425 430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
435 440 445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
450 455 460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465 470 475 480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
485 490 495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
500 505 510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
515 520 525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535 540

<210> 209

<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD220

<400> 209

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ala Gly Val Ile
    290                 295                 300

Ala Val Ile Val Val Val Val Ile Ala Val Val Ala Gly Ile Val Val
305                 310                 315                 320

Leu Val Ile Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
                325                 330                 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
            340                 345                 350
```

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
        355   360   365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 210
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD225

<400> 210

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140
```

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Leu Ile Ala Ala
    290   295   300

Gly Val Ile Gly Gly Leu Phe Ile Leu Val Ile Val Gly Leu Thr Phe
305   310   315   320

Ala Val Tyr Val Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
                325   330   335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys

            340   345   350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
        355   360   365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 211
<211> 541
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD244

<400> 211

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140
```

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 His Ile Ala Ser
    290   295   300

Ile Leu Ile Pro Leu Leu Leu Leu Leu Leu Leu Val Leu Val Ala Gly
305   310   315   320

Val Val Phe Trp Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser
                325   330   335

```
Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
            340                 345                 350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
        355                 360                 365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
    370                 375                 380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385                 390                 395                 400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
                405                 410                 415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
            420                 425                 430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
        435                 440                 445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
    450                 455                 460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465                 470                 475                 480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
                485                 490                 495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
            500                 505                 510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
        515                 520                 525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530                 535                 540
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<210> 212
<211> 541
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD247

<400> 212

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
```

130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Thr Asn Thr Val
290 295 300

Gly Ser Val Ile Gly Val Ile Val Thr Ile Phe Val Ser Gly Thr Val
305 310 315 320

Tyr Phe Ile Cys Gln Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser
325 330 335

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
340 345 350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
355 360 365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
370 375 380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385 390 395 400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
405 410 415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
420 425 430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
435 440 445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
450 455 460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465 470 475 480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
485 490 495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
500 505 510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
515 520 525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser

530 535 540

<210> 213
<211> 537
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD253

<400> 213

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Thr Leu Ile Ile
    290   295   300

Leu Ala Val Val Gly Gly Val Ile Gly Leu Leu Ile Leu Ile Leu Leu
305   310   315   320

Ile Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln Ala
                325   330   335

Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys Pro
            340   345   350

Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser Pro
        355   360   365

Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val Glu
    370   375   380

Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro Arg
385   390   395   400

Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile Lys
                405   410   415

Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp Ala
            420   425   430

Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr Leu
        435   440   445

Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser Asn
    450   455   460

Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser Gly
465   470   475   480

Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
                485   490   495

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
            500   505   510

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp
        515   520   525

Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 214
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD254

<400> 214

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

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Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ile Ile Gly Gly
    290                 295                 300

Val Ala Gly Ser Ile Leu Leu Val Leu Ile Val Val Gly Gly Ile Val
305                 310                 315                 320

Val Ala Leu Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
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325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
340 345 350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
355 360 365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
370 375 380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385 390 395 400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
405 410 415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
420 425 430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
435 440 445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
450 455 460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465 470 475 480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
485 490 495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
500 505 510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
515 520 525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 215
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD258

<400> 215

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

```
Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Leu Leu Tyr Leu
    290                 295                 300

Leu Ala Val Ala Val Val Ile Ile Leu Phe Ile Ile Leu Leu Gly Val
305                 310                 315                 320
```

Ile Met Ala Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
                325   330   335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
            340   345   350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
        355   360   365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
    370   375   380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385   390   395   400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
                405   410   415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
            420   425   430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
        435   440   445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
    450   455   460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465   470   475   480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
                485   490   495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
            500   505   510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
        515   520   525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 216
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD259

<400> 216

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

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

115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Leu Pro Leu Leu
290 295 300

Val Ala Gly Ala Val Leu Leu Leu Val Ile Leu Val Leu Gly Val Met
305 310 315 320

Val Ala Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu

515 520 525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 217
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD260

<400> 217

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Pro Val Leu Cys
290 295 300

Ser Pro Val Ala Gly Val Ile Leu Leu Ala Leu Gly Ala Leu Leu Val
305 310 315 320

Leu Gln Leu Ile Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
370 375 380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385 390 395 400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
405 410 415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
420 425 430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
435 440 445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
450 455 460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465 470 475 480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
485 490 495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
500 505 510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 218
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD260GV

<400> 218

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Pro Val Leu Cys
    290   295   300

Ser Pro Val Ala Gly Val Ile Leu Leu Ala Leu Gly Ala Leu Gly Val

305 310 315 320

Leu Gln Leu Ile Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
370 375 380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385 390 395 400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
405 410 415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
420 425 430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
435 440 445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
450 455 460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465 470 475 480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
485 490 495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
500 505 510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 219
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD268

<400> 219

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

```
Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Leu Leu Leu Ser
    290                 295                 300
```

```
Leu Ile Leu Val Ser Val Gly Phe Val Val Thr Val Phe Gly Val Ile
305                 310                 315                 320

Ile Phe Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325                 330                 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340                 345                 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355                 360                 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370                 375                 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385                 390                 395                 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405                 410                 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420                 425                 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435                 440                 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450                 455                 460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465                 470                 475                 480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485                 490                 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500                 505                 510
```

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 220
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD270

<400> 220

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu

100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Leu Ala Leu Gly
290 295 300

```
Ile Leu Gly Gly Leu Gly Thr Ala Ala Leu Leu Ile Gly Val Ile Leu
305                 310                 315                 320

Trp Gln Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325                 330                 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340                 345                 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355                 360                 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370                 375                 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385                 390                 395                 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405                 410                 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420                 425                 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435                 440                 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450                 455                 460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465                 470                 475                 480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485                 490                 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
```

500 505 510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
515 520 525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 221
<211> 537
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD270GVLVS

<400> 221

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

```
Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Leu Ala Leu Gly
    290                 295                 300
```

```
Ile Leu Gly Gly Leu Gly Thr Ala Ala Leu Leu Ile Gly Val Leu Val
305                 310                 315                 320

Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln Ala
                325                 330                 335

Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys Pro
            340                 345                 350

Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser Pro
        355                 360                 365

Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val Glu
    370                 375                 380

Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro Arg
385                 390                 395                 400

Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile Lys
                405                 410                 415

Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp Ala
            420                 425                 430

Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr Leu
        435                 440                 445

Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser Asn
    450                 455                 460

Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser Gly
465                 470                 475                 480

Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
                485                 490                 495
```

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
            500   505   510

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp
        515   520   525

Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 222
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD270LL

<400> 222

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Leu Ala Leu Gly

290 295 300

Ile Leu Gly Gly Leu Leu Leu Ala Ala Leu Leu Ile Gly Val Ile Leu
305 310 315 320

Trp Gln Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
325 330 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
340 345 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
355 360 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
370 375 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385 390 395 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
405 410 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
420 425 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
435 440 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
450 455 460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465 470 475 480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
485 490 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 223
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD272

<400> 223

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

```
Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ile Ala Gly Val
    290   295   300

Ile Ala Gly Ile Leu Leu Phe Val Ile Ile Phe Leu Gly Val Val Leu
305   310   315   320

Val Met Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 224
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD273

<400> 224

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser

85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ala Phe Ile Ala
    290   295   300

Gly Ile Gly Ala Ala Cys Trp Ile Ile Leu Met Val Phe Ser Ile Trp
305   310   315   320

Leu Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met

485 490 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
500 505 510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
515 520 525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 225
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD273GV

<400> 225

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Ala Phe Ile Ala
    290   295   300

Gly Ile Gly Ala Ala Cys Trp Ile Ile Leu Met Val Phe Ser Gly Val
305   310   315   320

Leu Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
485 490 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
500 505 510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
515 520 525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 226
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD273GVLLS

<400> 226

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Ala Phe Ile Ala
    290   295   300

Gly Ile Gly Ala Ala Cys Trp Ile Ile Leu Met Val Phe Ser Gly Val
305   310   315   320

Leu Leu Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
                325   330   335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
            340   345   350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
        355   360   365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
    370   375   380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385   390   395   400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
                405   410   415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
            420   425   430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
        435   440   445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
    450   455   460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465   470   475   480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
                485   490   495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
            500   505   510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
        515   520   525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 227
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD276

<400> 227

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ala Val Val Val
290 295 300

Pro Ile Leu Phe Leu Ile Leu Leu Ser Leu Gly Val Gly Phe Ala Ile
305 310 315 320

Leu Tyr Thr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
340 345 350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
355 360 365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
370 375 380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385 390 395 400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
405 410 415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
420 425 430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
435 440 445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
450 455 460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465 470 475 480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
                485   490   495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
            500   505   510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
        515   520   525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 228
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD277

<400> 228

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

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

65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Ser Val Pro Ile
290 295 300

Ile Leu Ala Ile Val Gly Leu Met Leu Val Thr Val Val Ala Gly Val
305 310 315 320

Leu Ile Val Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
340 345 350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
355 360 365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
370 375 380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385 390 395 400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
405 410 415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
420 425 430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
435 440 445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
450 455 460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly

465 470 475 480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
485 490 495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
500 505 510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
515 520 525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 229
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD278

<400> 229

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

```
Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270
```

Ser 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 Gly Val Ile Ala
    290   295   300

Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly Phe Met
305   310   315   320

Leu Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 230
<211> 541
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD279

<400> 230

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

```
Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
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260 265 270

Ser 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 Val Leu Ala Ala
290 295 300

Val Ile Ala Gly Gly Val Ile Gly Phe Leu Phe Ala Ile Phe Leu Ile
305 310 315 320

Leu Leu Leu Val Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser
325 330 335

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
340 345 350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
355 360 365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
370 375 380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385 390 395 400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
405 410 415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
420 425 430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
435 440 445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
450 455 460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465   470   475   480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
                485   490   495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
            500   505   510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
        515   520   525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 231
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD280

<400> 231

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

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Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Ala Val Ile Val
    290                 295                 300

Gly Gly Val Val Gly Ala Leu Phe Ala Ala Phe Leu Val Thr Leu Leu
305                 310                 315                 320

Ile Tyr Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325                 330                 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340                 345                 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355                 360                 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370                 375                 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385                 390                 395                 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405                 410                 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420                 425                 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435                 440                 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450                 455                 460
```

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 232
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD289

<400> 232

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu

50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

```
Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Met Tyr Pro Met
    290                 295                 300

Phe Leu Val Leu Leu Ala Leu Ala Val Leu Ala Leu Ala Ala Val Gly
305                 310                 315                 320

Val Val Val Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile
                325                 330                 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
            340                 345                 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
        355                 360                 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr
    370                 375                 380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385                 390                 395                 400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405                 410                 415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420                 425                 430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435                 440                 445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
```

450 455 460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465 470 475 480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
485 490 495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
500 505 510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
515 520 525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535 540

<210> 233
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD290

<400> 233

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Val Ile Thr Gly
    290   295   300

Ile Ile Leu Val Ile Ile Ala Leu Ala Phe Phe Gly Met Val Leu Ser
305   310   315   320

Thr Gln Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 234
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD291

<400> 234

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly

245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Pro Met Leu Ser
290 295 300

Met Leu Val Ile Pro Leu Leu Ile Ile Phe Val Phe Met Met Val Ile
305 310 315 320

Val Asn Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
325 330 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
340 345 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
355 360 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
370 375 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385 390 395 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
405 410 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
420 425 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
435 440 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 235
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD292

<400> 235

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

```
Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240
```

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Pro Met Tyr Val
290 295 300

Val Val Ala Ala Leu Val Leu Leu Ala Phe Ile Gly Val Gly Val Leu
305 310 315 320

Val Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
325 330 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
340 345 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
355 360 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
370 375 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385 390 395 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
405 410 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
420 425 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
435 440 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 236
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD295

<400> 236

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp

35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Leu Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
325 330 335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
340 345 350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
355 360 365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
370 375 380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385 390 395 400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
405 410 415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
420 425 430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr

435 440 445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
450 455 460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465 470 475 480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
485 490 495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
500 505 510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
515 520 525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
530 535

<210> 237
<211> 555
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD297pre

<400> 237

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

```
Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser Ile Glu
            340                 345                 350

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
        355                 360                 365

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
    370                 375                 380

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
385                 390                 395                 400

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
                405                 410                 415

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
            420                 425                 430
```

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
        435   440   445

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
    450   455   460

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
465   470   475   480

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
                485   490   495

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
            500   505   510

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
        515   520   525

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
    530   535   540

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
545   550   555

<210> 238
<211> 560
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD297pre_GV

<400> 238

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

```
His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
```

210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Gly Val Leu Leu Ser Arg Lys Arg Arg Arg Met Lys Leu
340 345 350

Leu Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu
355 360 365

Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn
370 375 380

Trp Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg
385 390 395 400

Ala His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu
405 410 415

Phe Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met
            420   425   430

Asp Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln
        435   440   445

Asp Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu
    450   455   460

Thr Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser
465   470   475   480

Ser Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser
                485   490   495

Ala Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp
            500   505   510

Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp
        515   520   525

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
    530   535   540

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
545   550   555   560

<210> 239
<211> 557
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pTMD297pre_GVLVS

<400> 239

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

```
Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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

Gly Val Leu Val Ser Arg Lys Arg Arg Arg Met Lys Leu Leu Ser Ser
            340                 345                 350

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
        355                 360                 365

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
    370                 375                 380

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
385                 390                 395                 400
```

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
                405   410   415

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
            420   425   430

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
        435   440   445

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
    450   455   460

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
465   470   475   480

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
                485   490   495

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
            500   505   510

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
        515   520   525

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
545   550   555

<210> 240
<211> 540
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS205

<400> 240

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175
```

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Phe Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser Lys Tyr Lys Gln Lys Pro Lys Met Lys Leu Leu Ser Ser Ile
325 330 335

Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys
340 345 350

Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg
355 360 365

Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr

    370   375   380

Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile
385   390   395   400

Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln
                405   410   415

Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn
            420   425   430

Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro
        435   440   445

Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu
    450   455   460

Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly
465   470   475   480

Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
                485   490   495

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
            500   505   510

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
        515   520   525

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 241
<211> 538
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS231

<400> 241

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175
```

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Phe Met Tyr Val
    290   295   300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305   310   315   320

Leu Ser Arg Arg Gln Arg Arg Met Lys Leu Leu Ser Ser Ile Glu Gln
                325   330   335

Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys
            340   345   350

Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser
        355   360   365

Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val
    370   375   380

Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro
385   390   395   400

Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile
                405   410   415

Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp
            420   425   430

Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr
        435   440   445

Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser
    450   455   460

Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser
465   470   475   480

Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
                485   490   495

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
            500   505   510

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
        515   520   525

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 242
<211> 541
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS262

<400> 242

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr

165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Phe Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser Arg Ser Arg Lys Val Asp Lys Arg Met Lys Leu Leu Ser Ser
325 330 335

Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser
340 345 350

Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys
355 360 365

Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu
    370   375   380

Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu
385   390   395   400

Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu
                405   410   415

Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val
            420   425   430

Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met
        435   440   445

Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu
    450   455   460

Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala
465   470   475   480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp
                485   490   495

Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met
            500   505   510

Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
        515   520   525

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 243
<211> 543
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS263

<400> 243

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145                 150                 155                 160
```

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Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165                 170                 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180                 185                 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195                 200                 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210                 215                 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225                 230                 235                 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245                 250                 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260                 265                 270

Ser 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 Phe Met Tyr Val
    290                 295                 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305                 310                 315                 320

Leu Ser Lys Arg Arg Asp Lys Glu Arg Gln Ala Lys Met Lys Leu Leu
                325                 330                 335

Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys
            340                 345                 350

Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp
        355                 360                 365
```

Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala
    370   375   380

His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe
385   390   395   400

Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp
                405   410   415

Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp
            420   425   430

Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr
        435   440   445

Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser
    450   455   460

Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala
465   470   475   480

Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp
                485   490   495

Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
            500   505   510

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
        515   520   525

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 244
<211> 545
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS266

<400> 244

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Phe Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser His Pro Leu Arg Lys Arg Arg Lys Arg Lys Lys Lys Met Lys
325 330 335

Leu Leu Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys
340 345 350

Leu Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn

355 360 365

Asn Trp Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr
370 375 380

Arg Ala His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln
385 390 395 400

Leu Phe Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys
405 410 415

Met Asp Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val
420 425 430

Gln Asp Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val
435 440 445

Glu Thr Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr
450 455 460

Ser Ser Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val
465 470 475 480

Ser Ala Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu
485 490 495

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe
500 505 510

Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
515 520 525

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
530 535 540

Ser
545

<210> 245
<211> 543
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS267

<400> 245

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130                 135                 140
```

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Phe Met Tyr Val
    290   295   300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305   310   315   320

Leu Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Met Lys Leu Leu
                325   330   335

Ser Ser Ile Glu Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys
            340   345   350

Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp
        355   360   365

Glu Cys Arg Tyr Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala
    370   375   380

His Leu Thr Glu Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe
385   390   395   400

Leu Leu Ile Phe Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp
                405   410   415

Ser Leu Gln Asp Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp
            420   425   430

Asn Val Asn Lys Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr
        435   440   445

Asp Met Pro Leu Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser
    450   455   460

Ser Glu Glu Ser Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala
465   470   475   480

Ala Ala Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp
                485   490   495

Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
            500   505   510

Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
        515   520   525

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535   540

<210> 246
<211> 537
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS268

<400> 246

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65                  70                  75                  80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100                 105                 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115                 120                 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
```

130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Phe Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser Lys Ile Phe Lys Met Lys Leu Leu Ser Ser Ile Glu Gln Ala
325 330 335

Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu Lys Pro
340 345 350

Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr Ser Pro
355 360 365

Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu Val Glu
370 375 380

Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe Pro Arg
385 390 395 400

Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp Ile Lys
405 410 415

Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys Asp Ala
420 425 430

Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu Thr Leu
435 440 445

Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser Ser Asn
450 455 460

Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly Ser Gly
465 470 475 480

Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
485 490 495

Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp
500 505 510

Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp
515 520 525

Asp Phe Asp Leu Asp Met Leu Gly Ser

530 535

<210> 247
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pSTS274

<400> 247

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
20 25 30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
35 40 45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
50 55 60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65 70 75 80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
85 90 95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
100 105 110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
115 120 125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145 150 155 160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
165 170 175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
180 185 190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
195 200 205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
210 215 220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225 230 235 240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
245 250 255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
260 265 270

Ser 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 Phe Met Tyr Val
290 295 300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305 310 315 320

Leu Ser Arg Arg Lys Arg Glu His Met Lys Leu Leu Ser Ser Ile Glu
325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
            340   345   350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
        355   360   365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
    370   375   380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385   390   395   400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
                405   410   415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
            420   425   430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
        435   440   445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
    450   455   460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465   470   475   480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
                485   490   495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
            500   505   510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
        515   520   525

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530   535

<210> 248
<211> 539
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic construct

<220>
<221> MISC_FEATURE
<223> pIZ364

<400> 248

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

His Ala Ala Arg Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asp
            20   25   30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35   40   45

Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu
    50   55   60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr
65   70   75   80

His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85   90   95

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln Glu
            100   105   110

Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr
        115   120   125

Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu Ser
145   150   155   160

Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr
                165   170   175

Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln
            180   185   190

Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu
        195   200   205

Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys
    210   215   220

Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr
225   230   235   240

Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly
                245   250   255

Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
            260   265   270

Ser 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 Phe Met Tyr Val
    290   295   300

Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu
305   310   315   320

Leu Ser Arg Arg Arg Arg Glu His Met Lys Leu Leu Ser Ser Ile Glu

325 330 335

Gln Ala Cys Asp Ile Cys Arg Leu Lys Lys Leu Lys Cys Ser Lys Glu
340 345 350

Lys Pro Lys Cys Ala Lys Cys Leu Lys Asn Asn Trp Glu Cys Arg Tyr
355 360 365

Ser Pro Lys Thr Lys Arg Ser Pro Leu Thr Arg Ala His Leu Thr Glu
370 375 380

Val Glu Ser Arg Leu Glu Arg Leu Glu Gln Leu Phe Leu Leu Ile Phe
385 390 395 400

Pro Arg Glu Asp Leu Asp Met Ile Leu Lys Met Asp Ser Leu Gln Asp
405 410 415

Ile Lys Ala Leu Leu Thr Gly Leu Phe Val Gln Asp Asn Val Asn Lys
420 425 430

Asp Ala Val Thr Asp Arg Leu Ala Ser Val Glu Thr Asp Met Pro Leu
435 440 445

Thr Leu Arg Gln His Arg Ile Ser Ala Thr Ser Ser Ser Glu Glu Ser
450 455 460

Ser Asn Lys Gly Gln Arg Gln Leu Thr Val Ser Ala Ala Ala Gly Gly
465 470 475 480

Ser Gly Gly Ser Gly Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
485 490 495

Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly
500 505 510

Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
515 520 525

```
Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
    530                 535
```