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(54) Title: ACTIVATABLE INTERLEUKIN 12 POLYPEPTIDES AND METHODS OF USE THEREOF

(57) Abstract: The disclosure features fusion proteins that are conditionally active variants of a cytokine of interest. In one aspect, the full-length polypeptides of the invention have reduced or minimal cytokine-receptor activating activity even though they contain a functional cytokine polypeptide. Upon activation, e.g., by cleavage of a linker that joins a blocking moiety, e.g. a steric blocking polypeptide, in sequence to the active cytokine, the cytokine can bind its receptor and effect signaling.

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ACTIVATABLE INTERLEUKIN 12 POLYPEPTIDES AND METHODS OF USE THEREOF**RELATED APPLICATIONS**

This application claims the benefit of U.S. Provisional Application 62/671,225, filed on May 14, 2018, U.S. Provisional Application No. 62/756,504, filed on November 6, 2018, and U.S. Provisional Application No. 62/756,515, filed on November 6, 2018. The entire teachings of the above applications are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing, which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 14, 2019, is named 105365-0022_SL.txt and is 232,520 bytes in size.

BACKGROUND

[1] The development of mature immunocompetent lymphoid cells from less-committed precursors, their subsequent antigen-driven immune responses, and the suppression of these and unwanted autoreactive responses are highly dependent and regulated by cytokines (including interleukin-2 [IL-2], IL-4, IL-7, IL-9, IL-15, and IL-21) that utilize receptors in the common γ -chain (γ_c) family (Rochman et al., 2009) and family members including IL-12, 18 and 23. IL-2 is essential for thymic development of Treg cells and critically regulates several key aspects of mature peripheral Treg and antigen-activated conventional T cells. Because of its potent T cell growth factor activity in vitro, IL-2 has been extensively studied in part because this activity offered a potential means to directly boost immunity, e.g., in cancer and AIDS-HIV patients, or a target to antagonize unwanted responses, e.g., transplantation rejection and autoimmune diseases. Although *in vitro* studies with IL-2 provided a strong rationale for these studies, the function of IL-2 in vivo is clearly much more complex as first illustrated in IL-2-deficient mice, where a rapid lethal autoimmune syndrome, not lack of immunity, was observed (Sadlack et al., 1993, 1995). Similar observations were later made when the gene encoding IL-2R α (Il2ra) and IL-2R β (Il2rb) were individually ablated (Suzuki et al., 1995; Willerford et al., 1995).

[2] The present invention refers to conditionally active and/or targeted cytokines for use in the treatment of cancer and other diseases dependent on immune up or down regulation. For example, the antitumoral activity of some cytokines is well known and described and some cytokines have already been used therapeutically in humans. Cytokines such as interleukin-2 (IL-2) and interferon α (IFN α) have shown positive antitumoral activity in patients with different types of tumors, such as kidney metastatic carcinoma, hairy cell leukemia, Kaposi sarcoma, melanoma, multiple myeloma, and the like. Other cytokines like IFN β , the Tumor Necrosis Factor (TNF) α , TNF β , IL-1, 4, 6, 12, 15 and the

CSFs have shown a certain antitumoral activity on some types of tumors and therefore are the object of further studies.

[2a] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

SUMMARY

[2b] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[2c] In a first aspect, the invention provides a fusion polypeptide of the formula:

[A]-[L1]-[D]-[L2]-[B] or [B]-[L1]-[A]-[L1]-[D]

wherein,

A is an interleukin 12 (IL-12) polypeptide;

B is a half-life extension element, wherein the half-life extension element is human serum albumin or an antigen-binding polypeptide that binds human serum albumin;

L1 is a protease-cleavable polypeptide linker, L2 is polypeptide linker that is optionally protease-cleavable, and when protease-cleavable L2 comprises at least one sequence that is cleavable by a protease, wherein for each of L1 and L2, independently, the protease is selected from the group consisting of a kallikrein, thrombin, chymase, carboxypeptidase A, an elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), a fibroblast activation protein (FAP), an ADAM metalloproteinase, a plasminogen activator, a cathepsin, a caspase, a tryptase, and a tumor cell surface protease; and

D is an IL-12 blocking moiety, wherein the blocking moiety is an antibody or antigen-binding fragment of an antibody that binds the IL-12 polypeptide; and wherein

the fusion polypeptide has attenuated IL-12 receptor activating activity, wherein the IL-12-receptor activating activity of the fusion polypeptide is at least about 10 fold less than the IL-12-receptor activating activity of the polypeptide that comprises the IL-12 polypeptide that is produced by cleavage of the protease-cleavable polypeptide linker L1 or, when L2 is protease-cleavable, by cleavage of both L1 and L2, and wherein the IL-12-receptor activating activity is assessed using a HEK Blue reporter cell assay, with equal amounts on a mole basis of the IL-12 polypeptide and the fusion polypeptide.

[2d] In a second aspect, the invention provides a nucleic acid encoding the polypeptide of the first aspect.

[2e] In a third aspect, the invention provides an isolated vector comprising the nucleic acid of the second aspect.

[2f] In a fourth aspect, the invention provides an isolated host cell comprising the vector of the third aspect.

[2g] In a fifth aspect, the invention provides a method of making a pharmaceutical composition, comprising culturing the host cell of the fourth aspect under suitable conditions for expression and collection of desired polypeptides.

[2h] In a sixth aspect, the invention provides a pharmaceutical composition comprising i) an effective amount of the fusion polypeptide of the first aspect, and ii) a pharmaceutically acceptable excipient.

[2i] In a seventh aspect, the invention provides a pharmaceutical composition comprising at least one of each of:

a) a human interleukin 12 (IL-12) polypeptide comprising an IL-12 subunit polypeptide selected from IL-12p35 and IL-12p40;

b) an IL-12 blocking moiety, wherein the IL-12 blocking moiety comprises a ligand-binding domain or fragment of a cognate receptor for the IL-12 polypeptide, or an antibody or antigen-binding fragment of an antibody that binds the IL-12 polypeptide;

c) a protease-cleavable polypeptide linker; and

d) a half-life extension element wherein the half-life extension element is human serum albumin, an antigen-binding polypeptide that binds human serum albumin, or an immunoglobulin Fc; wherein the IL-12 subunit polypeptide and the IL-12 blocking moiety are operably linked by the protease-cleavable polypeptide linker, the IL-12 polypeptide has attenuated IL-12-receptor activating activity at least about 10 fold less than the IL-12-receptor activating activity of the polypeptide that comprises the IL-12 polypeptide that is produced by cleavage of the protease-cleavable polypeptide linker, and wherein the IL-12 receptor activating activity is assessed using a HEK Blue reporter cell assay, with equal amounts on a mole basis of the IL-12 polypeptide and the pharmaceutical composition.

[3] Provided herein are therapeutic proteins, nucleic acids that encode the proteins, and compositions and methods of using the proteins and nucleic acids for the treatment of a disease or disorder, such as proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, graft-versus-host disease and the like.

[4] The invention features fusion proteins that are conditionally active variants of IL-12. In one aspect, the full-length polypeptides of the invention have reduced or minimal IL-12-receptor activating activity even though they contain a functional IL-12 polypeptide. Upon activation, e.g., by cleavage of a linker that joins a blocking moiety, e.g. a steric blocking polypeptide, in sequence to the active cytokine, IL-12, or a functional fragment or mutein thereof, can bind its receptor and effect signaling. If desired, the full-length polypeptides can include a blocking polypeptide moiety that also

provides additional advantageous properties. For example, the full-length polypeptide can contain a blocking polypeptide moiety that also extends the serum half-life and/or targets the full-length polypeptide to a desired site of cytokine activity. Alternatively, the full-length fusion polypeptides can contain a serum half-life extension element and/or targeting domain that are distinct from the blocking polypeptide moiety. Preferably, the fusion protein contains at least one element or domain capable of extending in vivo circulating half-life. Preferably, this element is removed enzymatically in the desired body location (e.g. protease cleavage in the tumor microenvironment), restoring pharmacokinetic properties to the payload molecule (e.g. IL2 or IFN α) substantially similar to the naturally occurring payload molecule. The fusion proteins are targeted to a desired cell or tissue. As described herein targeting is accomplished through the action of a blocking polypeptide moiety that also binds to a desired target, or through a targeting domain. The domain that recognizes a target antigen on a preferred target (for example a tumor-specific antigen), may be attached to the cytokine via a cleavable or non-cleavable linker. If attached by a non-cleavable linker, the targeting domain may further aid in retaining the cytokine in the tumor, and may be considered a retention domain. The targeting domain does not necessarily need to be directly linked to the payload molecule, and may be linked directly to another element of the fusion protein. This is especially true if the targeting domain is attached via a cleavable linker.

[5] In one aspect is provided a fusion polypeptide comprising an IL-12 polypeptide, or functional fragment or mutein thereof, and a blocking moiety, e.g. a steric blocking domain. The blocking moiety is fused to the IL-12 polypeptide, directly or through a linker, and can be separated from the IL-12 polypeptide by cleavage (e.g. protease mediate cleavage) of the fusion polypeptide at or near the fusion site or linker or in the blocking moiety. For example, when the IL-12 polypeptide is fused

[Text continues on page 3]

to a blocking moiety through a linker that contains a protease cleavage site, the IL-12 polypeptide is released from the blocking moiety and can bind its receptor, upon protease mediated cleavage of the linker. The linker is designed to be cleaved at the site of desired cytokine activity, for example in the tumor microenvironment, avoiding off-target cytokine activity and reducing overall toxicity of cytokine therapy.

[6] The blocking moiety can also function as a serum half-life extension element. In some embodiments, the fusion polypeptide further comprises a separate serum half-life extension element. In some embodiments, the fusion polypeptide further comprises a targeting domain. In various embodiments, the serum half-life extension element is a water-soluble polypeptide such as optionally branched or multi-armed polyethylene glycol (PEG), full length human serum albumin (HSA) or a fragment that preserves binding to FcRn, an Fc fragment, or a nanobody that binds to FcRn directly or to human serum albumin.

[7] In addition to serum half-life extension elements, the pharmaceutical compositions described herein preferably comprise at least one, or more targeting domains that bind to one or more target antigens or one or more regions on a single target antigen. It is contemplated herein that a polypeptide construct of the invention is cleaved, for example, in a disease-specific microenvironment or in the blood of a subject at the protease cleavage site and that the targeting domain(s) will bind to a target antigen on a target cell. At least one target antigen is involved in and/or associated with a disease, disorder or condition. Exemplary target antigens include those associated with a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease.

[8] In some embodiments, a target antigen is a cell surface molecule such as a protein, lipid or polysaccharide. In some embodiments, a target antigen is on a tumor cell, virally infected cell, bacterially infected cell, damaged red blood cell, arterial plaque cell, or fibrotic tissue cell.

[9] Target antigens, in some cases, are expressed on the surface of a diseased cell or tissue, for example a tumor or a cancer cell. Target antigens for tumors include but are not limited to Fibroblast activation protein alpha (FAPa), Trophoblast glycoprotein (5T4), Tumor-associated calcium signal transducer 2 (Trop2), Fibronectin EDB (EDB-FN), fibronectin EIIIB domain, CGS-2, EpCAM, EGFR, HER-2, HER-3, c-Met, FOLR1, and CEA. Pharmaceutical compositions disclosed herein, also include proteins comprising two antigen binding domains that bind to two different target antigens known to be expressed on a diseased cell or tissue. Exemplary pairs of antigen binding domains include but are not limited to EGFR/CEA, EpCAM/CEA, and HER-2/HER-3.

[10] In some embodiments, the targeting polypeptides independently comprise a scFv, a VH domain, a VL domain, a non-Ig domain, or a ligand that specifically binds to the target antigen. In some embodiments, the targeting polypeptides specifically bind to a cell surface molecule. In some embodiments, the targeting polypeptides specifically bind to a tumor antigen. In some embodiments,

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the targeting polypeptides specifically and independently bind to a tumor antigen selected from at least one of EpCAM, EGFR, HER-2, HER-3, cMet, CEA, and FOLR1. In some embodiments, the targeting polypeptides specifically and independently bind to two different antigens, wherein at least one of the antigens is a tumor antigen selected from EpCAM, EGFR, HER-2, HER-3, cMet, CEA, and FOLR1. In some embodiments, the targeting polypeptide serves as a retention domain and is attached to the cytokine via a non-cleavable linker.

[11] As described herein, the cytokine blocking moiety can bind to the cytokine and thereby block activation of the cognate receptor of the cytokine.

[12] This disclosure also related to nucleic acids, e.g., DNA, RNA, mRNA, that encode the conditionally active proteins described herein, as well as vectors and host cells that contain such nucleic acids.

[13] This disclosure also relates to pharmaceutical compositions that contain a conditionally active protein, nucleic acid that encodes the conditionally active protein, and vectors and host cells that contain such nucleic acids. Typically, the pharmaceutical composition contains one or more physiologically acceptable carriers and/or excipients.

[14] The disclosure also relates to therapeutic methods that include administering to a subject in need thereof an effective amount of a conditionally active protein, nucleic acid that encodes the conditionally active protein, vector or host cells that contain such a nucleic acid, and pharmaceutical compositions of any of the foregoing. Typically, the subject has, or is at risk of developing, a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease.

[15] The disclosure also relates to the use of a conditionally active protein, nucleic acid that encodes the conditionally active protein, vector or host cells that contain such a nucleic acid, and pharmaceutical compositions of any of the foregoing, for treating a subject in need thereof. Typically the subject has, or is at risk of developing, a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease.

[16] The disclosure also relates to the use of a conditionally active protein, nucleic acid that encodes the conditionally active protein, vector or host cells that contain such a nucleic acid for the manufacture of a medicament for treating a disease, such as a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, a graft-versus-host disease or a host-versus-graft disease.

BRIEF DESCRIPTION OF THE DRAWINGS

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[17] FIG. 1a is a schematic illustrating a protease-activated cytokine or chemokine that includes a blocking moiety. The blocking moiety may optionally function as a serum half-life extending domain. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety via a protease-cleavable linker, thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment a protease cleaves at a protease-cleavage site on the linker, releasing the blocking moiety and allowing the cytokine to bind to its receptor.

[18] FIG. 1b is a schematic illustrating a protease-activated cytokine or chemokine wherein HSA (blocking moiety) is directly bound to the cytokine or chemokine of interest, with a protease cleavage site between the HSA and a cytokine or chemokine of interest. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety via a protease-cleavable linker, thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment, the protease cleaves at a protease-cleavage site on linker, releasing the blocking moiety and allowing the cytokine to bind to its receptor.

[19] FIG. 1c is a schematic illustrating a protease-activated cytokine or chemokine wherein more than one HSA (blocking moiety) is bound directly to the molecule of interest. If desired, one or more of the HSA can be bonded to the cytokine or chemokine through a linker, such as a linker that contains a protease cleavage site. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety via a protease-cleavable linker, thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment, protease cleaves at protease-cleavage site on linker, releasing the blocking moiety and allowing cytokine to bind receptor. The cytokine now has similar pK properties as compared to the native cytokine (e.g., has a short half-life).

[20] FIG. 1d is a schematic illustrating a protease-activated cytokine or chemokine comprising more than one cytokine, of the same type or different type, each of which is bonded to a binding domain through a protease-cleavable linker. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety via a protease-cleavable linker, thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment a protease cleaves at a protease cleavage site on linker, releasing the blocking moiety and allowing the cytokine to bind to its receptor.

[21] FIG. 2 is a schematic illustrating a protease-activated cytokine or chemokine comprising a cytokine or chemokine polypeptide, a blocking moiety, and a serum half-life extending domain connected by at least one protease-cleavable linker. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety via protease-cleavable linkers, thus blocking its ability to bind to its receptor. It is also bound to a separate half-life extension element, which extends half-life in serum. To the right of the arrow the drawing shows that in an inflammatory or tumor environment a protease cleaves at a protease-cleavage site on linker, thus releasing the serum half-life extension

element and the blocking moiety and allowing the cytokine to bind to its receptor. The cytokine now has similar pK properties as compared to the native cytokine (e.g., a short half-life).

[22] **FIG. 3** is a schematic illustrating a protease-activated cytokine or chemokine comprising a cytokine or chemokine polypeptide, a blocking moiety, and a targeting domain connected by at least one protease-cleavable linker. To the left of the arrow the drawing shows that a cytokine is connected to a blocking moiety and a targeting domain via a protease-cleavable linker, thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor microenvironment a protease cleaves at the protease cleavage site in the linker, releasing the targeting domain and the blocking moiety and allowing the cytokine to bind to its receptor.

[23] **FIG. 4a** is a schematic illustrating a protease-activated cytokine or chemokine comprising a cytokine or chemokine polypeptide, a blocking moiety, a targeting domain, and a serum half-life extending domain connected by at least one protease-cleavable linker, wherein the cytokine polypeptide and the targeting domain are connected by a protease-cleavable linker. To the left of the arrow, the drawing shows that a is connected to targeting domain, blocking moiety, and half-life extension element via protease-cleavable linker(s), thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment, the protease cleaves at a protease-cleavage site on linker(s), releasing the half-life extension element, the targeting domain, and the blocking moiety, and allowing the cytokine to bind to its receptor. The cytokine now has similar pK properties as compared to the native cytokine (e.g., short half-life).

[24] **FIG. 4b** is a schematic illustrating a protease-activated cytokine or chemokine comprising a cytokine or chemokine polypeptide, a blocking moiety, a targeting domain, and a serum half-life extending domain connected by at least one protease-cleavable linker. To the left of the arrow, the drawing shows that a cytokine is connected to targeting domain, a blocking moiety, and a half-life extension element via protease-cleavable linker(s), thus blocking its ability to bind to its receptor. To the right of the arrow the drawing shows that in an inflammatory or tumor environment, the protease cleaves at a protease-cleavage site on linker(s), releasing the half-life extension element and the blocking moiety and allowing the cytokine to bind to the receptor. The targeting moiety remains bound, keeping the cytokine in the tumor microenvironment. The cytokine now has similar pK properties as compared to the native cytokine (e.g., a short half-life).

[25] **FIG. 5** is a schematic illustrating the structure of a variable domain of an immunoglobulin molecule. The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel. The CDRs are the loops that connect beta strands B-C, C'-C'', and F-G of the immunoglobulin fold, whereas the bottom loops that connect beta strands AB, CC', C''-D and E-F of the immunoglobulin fold, and the top loop that connects the D-E strands of the immunoglobulin fold are the non-CDR loops.

[26] **FIG. 6** is a schematic illustrating a protease-activated cytokine or chemokine comprising a

cytokine or chemokine polypeptide, a blocking moiety that is a serum albumin binding domain (e.g., a dAb), and a protease cleavable linker. In the illustrated example, the non-CDR loops in a serum albumin binding domain (e.g., a sdAb) can form a binding site for the cytokine IL-12. In this example, the binding site for serum albumin can be formed by the CDRs of the serum albumin binding domain.

[27] FIG. 7 is a graph depicting results from a HEK-Blue IL-12 reporter assay performed on human p40/murine p35 IL12 fusion proteins before and after protease cleavage. Analysis was performed based on quantification of Secreted Alkaline Phosphatase (SEAP) activity using the reagent QUANTI-Blue® (InvivoGen). Results confirm that IL12 protein fusion proteins are active.

[28] FIG. 8a-8f shows a series of graphs depicting the results of HEK-blue assay of four IL-12 fusion proteins, before and after cleavage by MMP9. Analysis was performed based on quantification of Secreted Alkaline Phosphatase (SEAP) activity using the reagent QUANTI-Blue (InvivoGen). The data show greater activity in the cleaved IL12 than in the full fusion protein. Constructs tested were ACP06 (FIG. 8a), ACP07 (FIG. 8c), ACP08 (FIG. 8b), ACP09 (FIG. 8d), ACP10 (FIG. 8e), ACP11 (FIG. 8f).

[29] FIG. 9 shows results of protein cleavage assay. Fusion protein ACP11 was run on an SDS-PAGE gel in both cleaved and uncleaved form. As can be seen in the gel, cleavage was complete.

[30] FIG. 10 is a schematic which depicts a non-limiting example of an inducible cytokine protein, wherein the construct is activated upon protease cleavage of a linker attached between two subunits of the cytokine.

[31] FIG. 11a-11d are graphs depicting results from a HEK-Blue assay performed on human p40/murine p35 IL12 fusion proteins before and after protease cleavage. The assay was performed. Results confirm that IL12 protein fusion proteins are active. Each proliferation assay was performed with HSA or without HSA.

FIG. 12 are two graphs showing activity of exemplary IFN γ fusion proteins (ACP51 and ACP52) cleaved by MMP9 protease compared to activity of uncleaved fusion proteins using B16 reporter assay. Each fusion protein comprises an anti-HSA binder and a tumor targeting domain.

[32] FIG. 13 is a series of graphs showing that cleaved IL-12 polypeptides are active in an HEKBlue reporter assay. The top left panel shows that murine IL-12 is active in this assay (positive control). The bottom left panel and the bottom right panel show the activity of uncut (squares) and cut (triangles), respectively. The EC50 values for each are shown in the table insert, top right panel.

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[33] FIG. 14 shows tumor volume over time in mice treated with 17.5µg ACP11 (squares), 175µg ACP11 (triangles), 525µg ACP11 (circles), and as controls 2µg ACP04 (dashed line, triangles) and 10 µg ACP04 (dashed line, diamonds). Vehicle alone is indicated by large open circles. The data show tumor volume decreasing over time in a dose-dependent manner in mice treated with both ACP11 and ACP04 (a human p40/murine p35 IL12 fusion protein).

[34] FIG. 15 is a series of spaghetti plots showing tumor volume over time in a mouse xenograft tumor model in mice each treated with vehicle alone (top left), 2µg ACP04 (top middle), 10µg ACP04 (top right), 17.5µg ACP11 (bottom left), 175µg ACP11 (bottom middle), and 525µg ACP11 (bottom right). Each line represents a single mouse.

[35] FIG. 16-21 illustrate the properties of TriTac polypeptides, which serve as exemplary protease cleavable fusion proteins.

DETAILED DESCRIPTION

[36] Disclosed herein are methods and compositions to engineer and use constructs comprising inducible IL-12. IL-12 is a potent immune agonist, which lead to it being considered a promising therapeutic agent for oncology. However, IL-12 and other cytokines proved to have a very narrow therapeutic window. Cytokines, such as IL-12, have short serum half-lives and are also considered to be highly potent. Consequently, therapeutic administration of cytokines produced undesirable systemic effects and toxicities. These were exacerbated by the need to administer large quantities of cytokine in order to achieve the desired levels of cytokine at the intended site of cytokine action (e.g., a tumor). Unfortunately, due to the biology of cytokines and inability to effectively target and control their activity, cytokines did not achieve the hoped-for clinical advantages in the treatment of tumors.

[37] Disclosed herein are fusion proteins that overcome the toxicity and short half-life problems that have severely limited the clinical use of IL-12 in oncology. The fusion proteins contain IL-12 polypeptides that have receptor agonist activity. But in the context of the fusion protein, the IL-12 receptor agonist activity is attenuated and the circulating half-life is extended. The fusion proteins include protease cleave sites, which are cleaved by proteases that are associated with a desired site of IL-12 activity (e.g., a tumor), and are typically enriched or selectively present at the site of desired

activity. Thus, the fusion proteins are preferentially (or selectively) and efficiently cleaved at the desired site of activity to limit cytokine activity substantially to the desired site of activity, such as the tumor microenvironment. Protease cleavage at the desired site of activity, such as in a tumor microenvironment, releases a form of IL-12 from the fusion protein that is much more active as a IL-12 receptor agonist than the fusion protein (typically at least about 100X more active than the fusion protein). The form of IL-12 that is released upon cleavage of the fusion protein typically has a short half-life, which is often substantially similar to the half-life of naturally occurring IL-12, further restricting IL-12 cytokine activity to the tumor microenvironment. Even though the half-life of the fusion protein is extended, toxicity is dramatically reduced or eliminated because the circulating fusion protein is attenuated and active cytokine is targeted to the tumor microenvironment. The fusion proteins described herein, for the first time, enable the administration of an effective therapeutic dose of a cytokine to treat tumors with the activity of the cytokine substantially limited to the tumor microenvironment, and dramatically reduces or eliminates unwanted systemic effects and toxicity of the cytokine.

[38] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a difference over what is generally understood in the art. The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodologies by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 4th ed. (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY. As appropriate, procedures involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer-defined protocols and conditions unless otherwise noted.

[39] “Cytokine” is a well-known term of art that refers to any of a class of immunoregulatory proteins (such as interleukin or interferon) that are secreted by cells especially of the immune system and that are modulators of the immune system. Cytokine polypeptides that can be used in the fusion proteins disclosed herein include, but are not limited to transforming growth factors, such as TGF- α and TGF- β (e.g., TGFbeta1, TGFbeta2, TGFbeta3); interferons, such as interferon- α , interferon- β , interferon- γ , interferon-kappa and interferon-omega; interleukins, such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-21 and IL-25; tumor necrosis factors, such as tumor necrosis factor alpha and lymphotoxin; chemokines (e.g., C-X-C motif chemokine 10 (CXCL10), CCL19, CCL20, CCL21), and granulocyte macrophage-colony stimulating factor (GM-CSF), as well as fragments of such polypeptides that activate the cognate receptors for the cytokine (i.e., functional fragments of the foregoing). “Chemokine” is a

term of art that refers to any of a family of small cytokines with the ability to induce directed chemotaxis in nearby responsive cells.

[40] Cytokines are well-known to have short serum half-lives that frequently are only a few minutes. Even forms of cytokines that have altered amino acid sequences intended to extend the serum half-life yet retain receptor agonist activity typically also have short serum half-lives. As used herein, a “short-half-life cytokine” refers to a cytokine that has a substantially brief half-life circulating in the serum of a subject, such as a serum half-life that is less than 10, less than 15, less than 30, less than 60, less than 90, less than 120, less than 240, or less than 480 minutes. As used herein, a short half-life cytokine includes cytokines which have not been modified in their sequence to achieve a longer than usual half-life in the body of a subject and polypeptides that have altered amino acid sequences intended to extend the serum half-life yet retain receptor agonist activity. This latter case is not meant to include the addition of heterologous protein domains, such as a bona fide half-life extension element, such as serum albumin. Typically a short half-life cytokine polypeptide, such as an IL-12 polypeptide has a serum half-life that is comparable to naturally occurring IL-12, e.g., within 5 fold, 4 fold, 3 fold or 2 fold of naturally occurring IL-12.

[41] “Sortases” are transpeptidases that modify proteins by recognizing and cleaving a carboxyl-terminal sorting signal embedded in or terminally attached to a target protein or peptide. Sortase A catalyzes the cleavage of the LPXTG motif (SEQ ID NO: 80) (where X is any standard amino acid) between the Thr and Gly residue on the target protein, with transient attachment of the Thr residue to the active site Cys residue on the enzyme, forming an enzyme-thioacyl intermediate. To complete transpeptidation and create the peptide-monomer conjugate, a biomolecule with an N-terminal nucleophilic group, typically an oligoglycine motif, attacks the intermediate, displacing Sortase A and joining the two molecules.

[42] As used herein, the term “steric blocker” refers to a polypeptide or polypeptide moiety that can be covalently bonded to a cytokine polypeptide directly or indirectly through other moieties such as linkers, for example in the form of a chimeric polypeptide (fusion protein), but otherwise does not covalently bond to the cytokine polypeptide. A steric blocker can non-covalently bond to the cytokine polypeptide, for example through electrostatic, hydrophobic, ionic or hydrogen bonding. A steric blocker typically inhibits or blocks the activity of the cytokine moiety due to its proximity to the cytokine moiety and comparative size.

[43] As used and described herein, a “half-life extension element” is a part of the chimeric polypeptide that increases the serum half-life and improve pK, for example, by altering its size (e.g., to be above the kidney filtration cutoff), shape, hydrodynamic radius, charge, or parameters of absorption, biodistribution, metabolism, and elimination.

[44] As used herein, the terms “activatable,” “activate,” “induce,” and “inducible” refer to the ability of a protein, i.e. a cytokine, that is part of a fusion protein, to bind its receptor and effectuate activity upon cleavage of additional elements from the fusion protein.

[45] As used herein, “plasmids” or “viral vectors” are agents that transport the disclosed nucleic acids into the cell without degradation and include a promoter yielding expression of the nucleic acid molecule and/or polypeptide in the cells into which it is delivered.

[46] As used herein, the terms “peptide”, “polypeptide”, or “protein” are used broadly to mean two or more amino acids linked by a peptide bond. Protein, peptide, and polypeptide are also used herein interchangeably to refer to amino acid sequences. It should be recognized that the term polypeptide is not used herein to suggest a particular size or number of amino acids comprising the molecule and that a peptide of the invention can contain up to several amino acid residues or more.

[47] As used throughout, “subject” can be a vertebrate, more specifically a mammal (e.g. a human, horse, cat, dog, cow, pig, sheep, goat, mouse, rabbit, rat, and guinea pig), birds, reptiles, amphibians, fish, and any other animal. The term does not denote a particular age or sex. Thus, adult and newborn subjects, whether male or female, are intended to be covered.

[48] As used herein, “patient” or “subject” may be used interchangeably and can refer to a subject with a disease or disorder (e.g. cancer). The term patient or subject includes human and veterinary subjects.

[49] As used herein the terms “treatment”, “treat”, or “treating” refers to a method of reducing the effects of a disease or condition or symptom of the disease or condition. Thus, in the disclosed method, treatment can refer to at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or substantially complete reduction in the severity of an established disease or condition or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus, the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition.

[50] As used herein, the terms “prevent”, “preventing”, and “prevention” of a disease or disorder refers to an action, for example, administration of the chimeric polypeptide or nucleic acid sequence encoding the chimeric polypeptide, that occurs before or at about the same time a subject begins to show one or more symptoms of the disease or disorder, which inhibits or delays onset or exacerbation of one or more symptoms of the disease or disorder.

[51] As used herein, references to “decreasing”, “reducing”, or “inhibiting” include a change of at least about 10%, of at least about 20%, of at least about 30%, of at least about 40%, of at least about 50%, of at least about 60%, of at least about 70%, of at least about 80%, of at least about 90% or greater as compared to a suitable control level. Such terms can include but do not necessarily include complete elimination of a function or property, such as agonist activity.

[52] An “attenuated cytokine receptor agonist” is a cytokine receptor agonist that has decreased

receptor agonist activity as compared to the cytokine receptor's naturally occurring agonist. An attenuated cytokine agonist may have at least about 10X, at least about 50X, at least about 100X, at least about 250X, at least about 500X, at least about 1000X or less agonist activity as compared to the receptor's naturally occurring agonist. When a fusion protein that contains a cytokine polypeptide as described herein is described as "attenuated" or having "attenuated activity", it is meant that the fusion protein is an attenuated cytokine receptor agonist.

[53] An "intact fusion protein" is a fusion protein in which no domain has been removed, for example by protease cleavage. A domain may be removable by protease cleavage or other enzymatic activity, but when the fusion protein is "intact", this has not occurred.

[54] As used herein "moiety" refers to a portion of a molecule that has a distinct function within that molecule, and that function may be performed by that moiety in the context of another molecule. A moiety may be a chemical entity with a particular function, or a portion of a biological molecule with a particular function. For example, a "blocking moiety" within a fusion protein is a portion of the fusion protein which is capable of blocking the activity of some or all of the fusion polypeptide. This may be a protein domain, such as serum albumin.

[55] In general, the therapeutic use of cytokines is strongly limited by their systemic toxicity. TNF, for example, was originally discovered for its capacity of inducing the hemorrhagic necrosis of some tumors, and for its in vitro cytotoxic effect on different tumoral lines, but it subsequently proved to have strong pro-inflammatory activity, which can, in case of overproduction conditions, dangerously affect the human body. As the systemic toxicity is a fundamental problem with the use of pharmacologically active amounts of cytokines in humans, novel derivatives and therapeutic strategies are now under evaluation, aimed at reducing the toxic effects of this class of biological effectors while keeping their therapeutic efficacy.

[56] Interleukin-12 (IL-12) is a disulfide-linked heterodimer of two separately encoded subunits (p35 and p40), which are linked covalently to give rise to the so-called bioactive heterodimeric (p70) molecule (Lieschke et al., 1997; Jana et al., 2014). Apart from forming heterodimers (IL-12 and IL-23), the p40 subunit is also secreted as a monomer (p40) and a homodimer (p40₂). It is known in the art that synthesis of the heterodimer as a single chain with a linker connecting the p35 to the p40 subunit preserves the full biological activity of the heterodimer. IL-12 plays a critical role in the early inflammatory response to infection and in the generation of Th1 cells, which favor cell-mediated immunity. It has been found that overproduction of IL-12 can be dangerous to the host because it is involved in the pathogenesis of a number of autoimmune inflammatory diseases (e.g. MS, arthritis, type 1 diabetes).

[57] The IL-12 receptor (IL-12R) is a heterodimeric complex consisting of IL-12Rβ1 and IL-12Rβ2 chains expressed on the surface of activated T-cells and natural killer cells (Trinchieri et al., 2003). The IL-12Rβ1 chain binds to the IL-12p40 subunit, whereas IL-12p35 in association with IL-

IL-12R β 2 confers an intracellular signaling ability (Benson et al., 2011). Signal transduction through IL-12R induces phosphorylation of Janus kinase (Jak2) and tyrosine kinase (Tyk2), that phosphorylate and activate signal transducer and activator of transcription (STAT)1, STAT3, STAT4, and STAT5. The specific cellular effects of IL-12 are due mainly to activation of STAT4. IL-12 induces natural killer and T-cells to produce cytokines, in particular interferon (IFN) γ , that mediate many of the proinflammatory activities of IL-12, including CD4⁺ T-cell differentiation toward the Th1 phenotype (Montepaone et al., 2014).

[58] IL-12 is a pleiotropic cytokine, the actions of which create an interconnection between the innate and adaptive immunity. IL-12 was first described as a factor secreted from PMA-induced EBV-transformed B-cell lines. Based on its actions, IL-12 has been designated as cytotoxic lymphocyte maturation factor and natural killer cell stimulatory factor. Due to bridging the innate and adaptive immunity and potentially stimulating the production of IFN γ , a cytokine coordinating natural mechanisms of anticancer defense, IL-12 seemed ideal candidate for tumor immunotherapy in humans. However, severe side effects associated with systemic administration of IL-12 in clinical investigations and the very narrow therapeutic index of this cytokine markedly tempered enthusiasm for the use of this cytokine in cancer patients (Lasek et. al., 2014). Approaches to IL-12 therapy in which delivery of the cytokine is tumor-targeted, which may diminish some of the previous issues with IL-12 therapy, are currently in clinical trials for cancers.

[59] The present invention is designed to address the shortcomings of direct IL-12 therapy and therapy using other cytokines, for example using cytokine blocking moieties, e.g. steric blocking polypeptides, serum half-life extending polypeptides, targeting polypeptides, linking polypeptides, including protease cleavable linkers, and combinations thereof. Cytokines, including interleukins (e.g., IL-2, IL-7, IL-12, IL-15, IL-18, IL-21 IL-23), interferons (IFNs, including IFN α , IFN β and IFN γ), tumor necrosis factors (e.g., TNF α , lymphotoxin), transforming growth factors (e.g., TGF β 1, TGF β 2, TGF β 3), chemokines (C-X-C motif chemokine 10 (CXCL10), CCL19, CCL20, CCL21), and granulocyte macrophage-colony stimulating factor (GM-CS) are highly potent when administered to patients. As used herein, “chemokine” means a family of small cytokines with the ability to induce directed chemotaxis in nearby responsive cells. Cytokines can provide powerful therapy, but are accompanied by undesired effects that are difficult to control clinically and which have limited the clinical use of cytokines. This disclosure relates to new forms of cytokines that can be used in patients with reduced or eliminated undesired effects. In particular, this disclosure relates to pharmaceutical compositions including chimeric polypeptides (fusion proteins), nucleic acids encoding fusion proteins and pharmaceutical formulations of the foregoing that contain cytokines or active fragments or muteins of cytokines that have decreased cytokine receptor activating activity in comparison to the corresponding cytokine. However, under selected conditions or in a selected biological environment the chimeric polypeptides activate their cognate receptors, often with the same or higher potency as the corresponding naturally occurring cytokine. As described herein, this is

typically achieved using a cytokine blocking moiety that blocks or inhibits the receptor activating function of the cytokine, active fragment or mutein thereof under general conditions but not under selected conditions, such as those present at the desired site of cytokine activity (e.g., an inflammatory site or a tumor).

[60] The chimeric polypeptides and nucleic acids encoding the chimeric polypeptides can be made using any suitable method. For example, nucleic acids encoding a chimeric polypeptide can be made using recombinant DNA techniques, synthetic chemistry or combinations of these techniques, and expressed in a suitable expression system, such as in CHO cells. Chimeric polypeptides can similarly be made, for example by expression of a suitable nucleic acid, using synthetic or semi-synthetic chemical techniques, and the like. In some embodiments, the blocking moiety can be attached to the cytokine polypeptide via sortase-mediated conjugation. "Sortases" are transpeptidases that modify proteins by recognizing and cleaving a carboxyl-terminal sorting signal embedded in or terminally attached to a target protein or peptide. Sortase A catalyzes the cleavage of the LPXTG motif (SEQ ID NO: 80) (where X is any standard amino acid) between the Thr and Gly residue on the target protein, with transient attachment of the Thr residue to the active site Cys residue on the enzyme, forming an enzyme-thioacyl intermediate. To complete transpeptidation and create the peptide-monomer conjugate, a biomolecule with an N-terminal nucleophilic group, typically an oligoglycine motif, attacks the intermediate, displacing Sortase A and joining the two molecules.

[61] To form the cytokine-blocking moiety fusion protein, the cytokine polypeptide is first tagged at the N-terminus with a polyglycine sequence, or alternatively, with at the C-terminus with a LPXTG motif (SEQ ID NO: 80). The blocking moiety or other element has respective peptides attached that serve as acceptor sites for the tagged polypeptides. For conjugation to domains carrying a LPXTG (SEQ ID NO: 80) acceptor peptide attached via its N-terminus, the polypeptide will be tagged with an N-terminal poly-glycine stretch. For conjugation to domain carrying a poly-glycine peptide attached via its C-terminus, the polypeptide will be tagged at its C-terminus with a LPXTG (SEQ ID NO: 80) sortase recognition sequence. Recognizing poly-glycine and LPXTG (SEQ ID NO: 80) sequences, sortase will form a peptide bond between polymer-peptide and tagged polypeptides. The sortase reaction cleaves off glycine residues as intermediates and occurs at room temperature.

[62] A variety of mechanisms can be exploited to remove or reduce the inhibition caused by the blocking moiety. For example, the pharmaceutical compositions can include an IL-12 polypeptide and a blocking moiety, e.g. a steric blocking moiety, with a protease cleavable linker comprising a protease cleavage site located between the IL-12 polypeptide and cytokine blocking moiety or within the cytokine blocking moiety. When the protease cleavage site is cleaved, the blocking moiety can dissociate from cytokine, and the cytokine can then activate cytokine receptor.

[63] Any suitable linker can be used. For example, the linker can comprise glycine-glycine, a sortase-recognition motif, or a sortase-recognition motif and a peptide sequence $(\text{Gly}_4\text{Ser})_n$ (SEQ ID NO: 81) or $(\text{Gly}_3\text{Ser})_n$ (SEQ ID NO: 82), wherein n is 1, 2, 3, 4 or 5. Typically, the sortase-

recognition motif comprises a peptide sequence LPXTG (SEQ ID NO: 80), where X is any amino acid. In some embodiments, the covalent linkage is between a reactive lysine residue attached to the C-terminal of the cytokine polypeptide and a reactive aspartic acid attached to the N-terminal of the blocker or other domain. In other embodiments, the covalent linkage is between a reactive aspartic acid residue attached to the N-terminal of the cytokine polypeptide and a reactive lysine residue attached to the C-terminal of said blocker or other domain.

[64] Accordingly, as described in detail herein, the cytokine blocking moieties (IL-12 blocking moieties) used can be steric blockers. As used herein, a “steric blocker” refers to a polypeptide or polypeptide moiety that can be covalently bonded to a cytokine polypeptide directly or indirectly through other moieties such as linkers, for example in the form of a chimeric polypeptide (fusion protein), but otherwise does not covalently bond to the cytokine polypeptide. A steric blocker can non-covalently bond to the cytokine polypeptide, for example through electrostatic, hydrophobic, ionic or hydrogen bonding. A steric blocker typically inhibits or blocks the activity of the cytokine moiety due to its proximity to the cytokine moiety and comparative size. The steric inhibition of the cytokine moiety can be removed by spatially separating the cytokine moiety from the steric blocker, such as by enzymatically cleaving a fusion protein that contains a steric blocker and a cytokine polypeptide at a site between the steric blocker and the cytokine polypeptide.

[65] As described in greater detail herein, the blocking function can be combined with or due to the presence of additional functional components in the pharmaceutical composition, such as a targeting domain, a serum half-life extension element, and protease-cleavable linking polypeptides. For example, a serum half-life extending polypeptide can also be a steric blocker.

[66] Various elements ensure the delivery and activity of IL-12 preferentially at the site of desired IL-12 activity and to severely limit systemic exposure to the interleukin via a blocking and/or a targeting strategy preferentially linked to a serum half-life extension strategy. In this serum half-life extension strategy, the blocked version of interleukin circulates for extended times (preferentially 1-2 or more weeks) but the activated version has the typical serum half-life of the interleukin.

[67] In some embodiments of this invention, the half-life extension element is linked to the interleukin via a linker which is cleaved at the site of action (e.g. by inflammation-specific or tumor-specific proteases) releasing the interleukin’s full activity at the desired site and also separating it from the half-life extension of the uncleaved version. In such embodiments, the fully active and free interleukin would have very different pharmacokinetic (pK) properties – a half-life of hours instead of weeks. In addition, exposure to active cytokine is limited to the site of desired cytokine activity (e.g., an inflammatory site or tumor) and systemic exposure to active cytokine, and associated toxicity and side effects, are reduced.

[68] Blocking moieties, described in further detail below, can also be used to favor binding to or activation of one or more receptors. This blocking may be relievable by removal of the blocking

moieties in a particular environment, for example by proteolytic cleavage of a linker linking one or more blocking moieties to the cytokine.

[69] In another aspect, a similar approach can be applied to improve other cytokines, particularly for use as immunostimulatory agents, for example for treating cancer. For example, in this aspect, the pharmacokinetics and/or pharmacodynamics of the cytokine (e.g., IL-2, IL-7, IL-12, IL-15, IL-18, IL-21, IL-23, IFN α , IFN β and IFN γ , TNF α , lymphotoxin, TGF β 1, TGF β 2, TGF β 3, GM-CSF, CXCL10, CCL19, CCL20, and CCL21) can be tailored to maximally activate effector cells (e.g., effect T cells, NK cells) and/or cytotoxic immune response promoting cells (e.g., induce dendritic cell maturation) at a site of desired activity, such as in a tumor, but preferably not systemically.

[70] Thus, provided herein are pharmaceutical compositions comprising at least one cytokine polypeptide, such as interleukins (e.g., IL-2, IL-7, IL-12, IL-15, IL-18, IL-21, IL-23), interferons (IFNs, including IFN α , IFN β and IFN γ), tumor necrosis factors (e.g., TNF α , lymphotoxin), transforming growth factors (e.g., TGF β 1, TGF β 2, TGF β 3), chemokines (e.g., CXCL10, CCL19, CCL20, CCL21) and granulocyte macrophage-colony stimulating factor (GM-CS) or a functional fragment or mutein of any of the foregoing. The polypeptide typically also includes at least one linker amino acid sequence, wherein the amino acid sequence is in certain embodiments capable of being cleaved by an endogenous protease. In one embodiment, the linker comprises an amino acid sequence comprising HSSKLQ (SEQ ID NO: 24), GPLGVRG (SEQ ID NO: 83), IPVSLRSG (SEQ ID NO: 84), VPLSLYSG (SEQ ID NO: 85), or SGESPAYYTA (SEQ ID NO: 86). In other embodiments, the chimeric polypeptide further contains a blocking moiety, e.g. a steric blocking polypeptide moiety, capable of blocking the activity of the interleukin polypeptide. The blocking moiety, for example, can comprise a human serum albumin (HSA) binding domain or an optionally branched or multi-armed polyethylene glycol (PEG). Alternatively, the pharmaceutical composition comprises a first cytokine polypeptide or a fragment thereof, and blocking moiety, e.g. a steric blocking polypeptide moiety, wherein the blocking moiety blocks the activity of the cytokine polypeptide on the cytokine receptor, and wherein the blocking moiety in certain embodiments comprises a protease cleavable domain. In some embodiments, blockade and reduction of cytokine activity is achieved simply by attaching additional domains with very short linkers to the N or C terminus of the interleukin domain. In such embodiments, it is anticipated the blockade is relieved by protease digestion of the blocking moiety or of the short linker that tethers the blocker to the interleukin. Once the domain is clipped or is released, it will no longer be able to achieve blockade of cytokine activity.

[71] The pharmaceutical composition e.g., chimeric polypeptide can comprise two or more cytokines, which can be the same cytokine polypeptide or different cytokine polypeptides. For example, the two or more different types of cytokines have complementary functions. In some examples, a first cytokine is IL-12 and a second cytokine is IL-2. In some embodiments, each of the

two or more different types of cytokine polypeptides have activities that modulate the activity of the other cytokine polypeptides. In some examples of chimeric polypeptides that contain two cytokine polypeptides, a first cytokine polypeptide is T-cell activating, and a second cytokine polypeptide is non-T-cell-activating. In some examples of chimeric polypeptides that contain two cytokine polypeptides, a first cytokine is a chemoattractant, e.g. CXCL10, and a second cytokine is an immune cell activator.

[72] Preferably, the IL-12 polypeptides (including functional fragments) that are included in the fusion proteins disclosed herein are not mutated or engineered to alter the properties of the naturally occurring cytokine, including receptor binding affinity and specificity or serum half-life. However, changes in amino acid sequence from naturally occurring (including wild type) cytokine are acceptable to facilitate cloning and to achieve desired expression levels, for example.

Blocking Moiety

[73] The blocking moiety can be any moiety that inhibits the ability of the cytokine to bind and/or activate its receptor. The blocking moiety can inhibit the ability of the cytokine to bind and/or activate its receptor sterically blocking and/or by noncovalently binding to the cytokine. Examples of suitable blocking moieties include the full length or a cytokine-binding fragment or mutein of the cognate receptor of the cytokine. Antibodies and fragments thereof including, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody a single chain variable fragment (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain of camelid-type nanobody (VHH), a dAb and the like that bind the cytokine can also be used. Other suitable antigen-binding domain that bind the cytokine can also be used, include non-immunoglobulin proteins that mimic antibody binding and/or structure such as, anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPin, fynomers, kunitz domain peptides, monobodies, and binding domains based on other engineered scaffolds such as SpA, GroEL, fibronectin, lipocalin and CTLA4 scaffolds. Further examples of suitable blocking polypeptides include polypeptides that sterically inhibit or block binding of the cytokine to its cognate receptor. Advantageously, such moieties can also function as half-life extending elements. For example, a peptide that is modified by conjugation to a water-soluble polymer, such as PEG, can sterically inhibit or prevent binding of the cytokine to its receptor. Polypeptides, or fragments thereof, that have long serum half-lives can also be used, such as serum albumin (human serum albumin), immunoglobulin Fc, transferrin and the like, as well as fragments and muteins of such polypeptides. Antibodies and antigen-binding domains that bind to, for example, a protein with a long serum half-life such as HSA, immunoglobulin or transferrin, or to a receptor that is recycled to the plasma membrane, such as FcRn or transferrin receptor, can also inhibit the cytokine, particularly when bound to their antigen. Examples of such antigen-binding polypeptides include a single chain variable fragment (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light chain

variable domain (VL) and a variable domain of camelid-type nanobody (VHH), a dAb and the like. Other suitable antigen-binding domain that bind the cytokine can also be used, include non-immunoglobulin proteins that mimic antibody binding and/or structure such as, anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPin, fynomers, kunitz domain peptides, monobodies, and binding domains based on other engineered scaffolds such as SpA, GroEL, fibronectin, lipocalin and CTLA4 scaffolds.

[74] In illustrative examples, when IL-12 is the cytokine in the chimeric polypeptide, the blocking moiety can be the full length or fragment or mutein of the first molecule of IL-12 receptor (IL-12R β 1) or beta (IL-12R β 2), an anti-IL-2 single-domain antibody (dAb) or scFv, an anti-IL-12R β 1 antibody or fragment thereof, an anti-IL-12R β 2 antibody or fragment thereof, and anti-HSA dAb or scFv, and the like.

Additional aspects of the invention

1. A fusion protein comprising a cytokine moiety that is operably linked to a binding moiety, the binding moiety comprising a non-CDR loop and a cleavable linker, wherein the binding moiety is capable of masking the binding the cytokine to its receptor and/or the activation of the receptor by the cytokine.
2. The fusion protein of aspect 1, wherein the binding moiety is a natural peptide, a synthetic peptide, an engineered scaffold, or an engineered bulk serum protein.
3. The fusion protein of aspect 1 or 2, wherein the engineered scaffold comprises a sdAb, a scFv, a Fab, a VHH, a fibronectin type III domain, immunoglobulin-like scaffold, DARPin, cystine knot peptide, lipocalin, three-helix bundle scaffold, protein G-related albumin-binding module, or a DNA or RNA aptamer scaffold.
4. The fusion protein of any one of aspects 1-2, wherein the binding moiety is capable of binding to a bulk serum protein.
5. The fusion protein of any one of aspects 1-3, wherein the non-CDR loop is from a variable domain, a constant domain, a C1-set domain, a C2-set domain, an I-domain, or any combinations thereof.
6. The fusion protein of any one of aspects 1-4, wherein the binding moiety further comprises complementarity determining regions (CDRs).
7. The fusion protein of aspect 5, wherein the binding moiety is capable of binding to the bulk serum protein.
8. The fusion protein of aspect 6, wherein the bulk serum protein is a half-life extending protein.
9. The fusion protein of aspect 6 or 7, wherein the bulk serum protein is albumin, transferrin, Factor XIII, or Fibrinogen.
10. The fusion protein of any one of aspects 5-8, wherein the CDR loop provides the binding site specific for the bulk serum protein or the immunoglobulin light chain, or any combinations thereof.

11. The fusion protein of any one of aspects 1-9, wherein the cleavable linker comprises a cleavage site.
12. The fusion protein of aspect 10, wherein the cleavage site is recognized by a protease.
13. The fusion protein of aspect 11, wherein the binding moiety is bound to the cytokine.
14. The fusion protein of aspect 11 or 11, wherein the binding moiety is covalently linked to the cytokine.
15. The fusion protein of aspect 11, 11, or 14, wherein the binding moiety is capable of masking the binding of the cytokine to its target via specific intermolecular interactions between the binding moiety and the cytokine.
16. The fusion protein of any one of aspects 11-14, wherein the non-CDR loop provides a binding site specific for binding of the moiety to the cytokine.
17. The fusion protein of any one of aspects 11-15, wherein upon cleavage of the cleavable linker, the binding moiety is separated from the cytokine and the cytokine binds to its target.
18. The fusion protein of any one of aspects 1-16, wherein the cytokine binds to a cytokine receptor.
19. The fusion protein of aspect 17, wherein the cytokine receptor comprises a type I cytokine receptor, a type I IL receptor, a type II IL receptor, a chemokine receptor, or a tumor necrosis receptor superfamily receptor.
20. The fusion protein of any one of aspects 1-18, wherein the cleavable linker comprises a cleavage site.
21. The fusion protein of aspect 20, wherein the cleavage site is recognized by a protease.
22. The fusion protein of aspect 21, wherein the protease cleavage site is recognized by a serine protease, a cysteine protease, an aspartate protease, a threonine protease, a glutamic acid protease, a metalloproteinase, a gelatinase, or an asparagine peptide lyase.
23. The fusion protein of aspect 21, wherein the protease cleavage site is recognized by a Cathepsin B, a Cathepsin C, a Cathepsin D, a Cathepsin E, a Cathepsin K, a Cathepsin L, a kallikrein, a hK1, a hK10, a hK15, a plasmin, a collagenase, a Type IV collagenase, a stromelysin, a Factor Xa, a chymotrypsin-like protease, a trypsin-like protease, a elastase-like protease, a subtilisin-like protease, an actinidain, a bromelain, a calpain, a caspase, a caspase-3, a Mir1-CP, a papain, a HIV-1 protease, a HSV protease, a CMV protease, a chymosin, a renin, a pepsin, a matriptase, a legumain, a plasmepsin, a nepenthesin, a metalloexopeptidase, a metalloendopeptidase, a matrix metalloprotease (MMP), a MMP1, a MMP2, a MMP3, a MMP8, a MMP9, a MMP10, a MMP11, a MMP12, a MMP13, a MMP14, an ADAM10, an ADAM17, an ADAM12, an urokinase plasminogen activator (uPA), an enterokinase, a prostate-specific target (PSA, hK3), an interleukin-1 β converting enzyme, a thrombin, a FAP (FAP- α), a dipeptidyl peptidase, or dipeptidyl peptidase IV (DPPIV/CD26), a type II transmembrane serine protease (TTSP), a neutrophil elastase, a cathepsin G, a proteinase 3, a neutrophil serine protease 4, a mast cell

chymase, a mast cell tryptase, a dipeptidyl peptidase, and a dipeptidyl peptidase IV (DPPIV/CD26).

24. A conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cytokine, and a cleavable linker (L), wherein the non-CDR loop is capable of binding to the cytokine, and wherein the binding moiety is capable of inhibiting the binding of the cytokine to its receptor and/or inhibiting activation of the receptor by the cytokine.
25. The conditionally active binding protein of aspect 24, wherein the binding moiety is capable of binding to a half-life extending protein.
26. The conditionally active binding protein of aspect 24 or 25, wherein the binding moiety is a natural peptide, a synthetic peptide, an engineered scaffold, or an engineered serum bulk protein.
27. The conditionally active binding protein of aspect 26, wherein the engineered scaffold comprises a sdAb, a scFv, a Fab, a VHH, a fibronectin type III domain, immunoglobulin-like scaffold, DARPin, cystine knot peptide, lipocalin, three-helix bundle scaffold, protein G-related albumin-binding module, or a DNA or RNA aptamer scaffold.
28. The conditionally active binding protein of any one of aspects 24-27, wherein the non-CDR-loop is from a variable domain, a constant domain, a C1-set domain, a C2-set domain, an I-domain, or any combinations thereof.
29. The conditionally active binding protein of any one of aspects 24-28, wherein the binding moiety further comprises complementarity determining regions (CDRs).
30. The conditionally active binding protein of any one of aspects 24-29, wherein the binding moiety comprises a binding site specific for a bulk serum protein.
31. The conditionally active binding protein of aspect 30, wherein the bulk serum protein is albumin, transferrin, Factor XIII, or Fibrinogen.
32. The conditionally active binding protein of any one of aspects 29-31, wherein the CDRs provide the binding site specific for the bulk serum protein or the immunoglobulin light chain, or any combinations thereof.
33. The conditionally active binding protein of any one of aspects 29-32, wherein the binding moiety is capable of masking the binding of the cytokine to its target via specific intermolecular interactions between the binding moiety and the cytokine.
34. The conditionally active binding protein of any one of aspects 29-33, wherein the non-CDR loop provides a binding site specific for binding of the binding moiety to the cytokine.
35. The conditionally active binding protein of any one of aspects 24-34, wherein the cytokine binds to a cytokine receptor.
36. The conditionally active binding protein of aspect 35, wherein the cytokine receptor comprises a type I cytokine receptor, a type I IL receptor, a type II IL receptor, a chemokine receptor, or a tumor necrosis receptor superfamily receptor.

37. The conditionally active binding protein of aspect 24-36, wherein the cleavable linker comprises a cleavage site.
38. The conditionally active binding protein of aspect 37, wherein the cleavage site is recognized by a protease.
39. The conditionally active binding protein of aspect 38, wherein the protease cleavage site is recognized by a serine protease, a cysteine protease, an aspartate protease, a threonine protease, a glutamic acid protease, a metalloproteinase, a gelatinase, or an asparagine peptide lyase.
40. The conditionally active binding protein of aspect 38, wherein the protease cleavage site is recognized by a Cathepsin B, a Cathepsin C, a Cathepsin D, a Cathepsin E, a Cathepsin K, a Cathepsin L, a kallikrein, a hK1, a hK10, a hK15, a plasmin, a collagenase, a Type IV collagenase, a stromelysin, a Factor Xa, a chymotrypsin-like protease, a trypsin-like protease, a elastase-like protease, a subtilisin-like protease, an actinidain, a bromelain, a calpain, a caspase, a caspase-3, a Mir1-CP, a papain, a HIV-1 protease, a HSV protease, a CMV protease, a chymosin, a renin, a pepsin, a matriptase, a legumain, a plasmepsin, a nepenthesin, a metalloexopeptidase, a metalloendopeptidase, a matrix metalloprotease (MMP), a MMP1, a MMP2, a MMP3, a MMP8, a MMP9, a MMP10, a MMP11, a MMP12, a MMP13, a MMP14, an ADAM10, an ADAM17, an ADAM12, an urokinase plasminogen activator (uPA), an enterokinase, a prostate-specific target (PSA, hK3), an interleukin-1 β converting enzyme, a thrombin, a FAP (FAP- α), a dipeptidyl peptidase, or dipeptidyl peptidase IV (DPPIV/CD26), a type II transmembrane serine protease (TTSP), a neutrophil elastase, a cathepsin G, a proteinase 3, a neutrophil serine protease 4, a mast cell chymase, a mast cell tryptase, a dipeptidyl peptidase, and a dipeptidyl peptidase IV (DPPIV/CD26).
41. The conditionally active binding protein of aspect 24, further comprising a half-life extension domain bound to the binding moiety, wherein the half-life extension domain provides the binding protein with a safety switch, and wherein upon cleavage of the linker the binding protein is activated by separation of the binding moiety and the half-life extension domain from the cytokine, and the binding protein is thereby separated from the safety switch.
42. The conditionally active binding protein of aspect 41, wherein the cleavage of the linker is in a tumor microenvironment.
43. A conditionally active binding protein, comprising a binding moiety that binds a cytokine via a non-CDR loop within the binding moiety, wherein the binding moiety is further linked to a half-life extension domain and comprises a cleavable linker, wherein the binding protein has an extended half-life prior to its activation by cleavage of the linker, and wherein upon activation the binding moiety and the half-life extension domain are separated from the cytokine, and wherein the binding protein, in its activated state, does not have an extended half-life.
44. The conditionally active binding protein of aspect 43, wherein the cleavage of the linker is in a tumor microenvironment.

In vivo Half-life Extension Elements

[75] Preferably, the chimeric polypeptides comprise an in vivo half-life extension element. Increasing the in vivo half-life of therapeutic molecules with naturally short half-lives allows for a more acceptable and manageable dosing regimen without sacrificing effectiveness. As used herein, a “half-life extension element” is a part of the chimeric polypeptide that increases the in vivo half-life and improve pK, for example, by altering its size (e.g., to be above the kidney filtration cutoff), shape, hydrodynamic radius, charge, or parameters of absorption, biodistribution, metabolism, and elimination. An exemplary way to improve the pK of a polypeptide is by expression of an element in the polypeptide chain that binds to receptors that are recycled to the plasma membrane of cells rather than degraded in the lysosomes, such as the FcRn receptor on endothelial cells and transferrin receptor. Three types of proteins, e.g., human IgGs, HSA (or fragments), and transferrin, persist for much longer in human serum than would be predicted just by their size, which is a function of their ability to bind to receptors that are recycled rather than degraded in the lysosome. These proteins, or fragments of them that retain the FcRn binding are routinely linked to other polypeptides to extend their serum half-life. In one embodiment, the half-life extension element is a human serum albumin (HSA) binding domain. HSA (SEQ ID NO: 1) may also be directly bound to the pharmaceutical compositions or bound via a short linker. Fragments of HSA may also be used. HSA and fragments thereof can function as both a blocking moiety and a half-life extension element. Human IgGs can also carry out a similar function.

[76] The serum half-life extension element can also be antigen-binding polypeptide that binds to a protein with a long serum half-life such as serum albumin, transferrin and the like. Examples of such polypeptides include antibodies and fragments thereof including, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody a single chain variable fragment (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain of camelid-type nanobody (VHH), a dAb and the like. Other suitable antigen-binding domain include non-immunoglobulin proteins that mimic antibody binding and/or structure such as, anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPins, fynomers, kunitz domain peptides, monobodies, and binding domains based on other engineered scaffolds such as SpA, GroEL, fibronectin, lipocalin and CTLA4 scaffolds. Further examples of antigen-binding polypeptides include a ligand for a desired receptor, a ligand-binding portion of a receptor, a lectin, and peptides that binds to or associates with one or more target antigens.

[77] Some preferred serum half-life extension elements are polypeptides that comprise complementarity determining regions (CDRs), and optionally non-CDR loops. Advantageously, such serum half-life extension elements can extend the serum half-life of the cytokine, and also function as inhibitors of the cytokine (e.g., via steric blocking, non-covalent interaction or combination thereof) and/or as targeting

domains. In some instances, the serum half-life extension elements are domains derived from an immunoglobulin molecule (Ig molecule) or engineered protein scaffolds that mimic antibody structure and/or binding activity. The Ig may be of any class or subclass (IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM etc). A polypeptide chain of an Ig molecule folds into a series of parallel beta strands linked by loops. In the variable region, three of the loops constitute the "complementarity determining regions" (CDRs) which determine the antigen binding specificity of the molecule. An IgG molecule comprises at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding fragment thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs) which are hypervariable in sequence and/or involved in antigen recognition and/or usually form structurally defined loops, interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some embodiments of this disclosure, at least some or all of the amino acid sequences of FR1, FR2, FR3, and FR4 are part of the "non-CDR loop" of the binding moieties described herein. As shown in **Fig. 5**, a variable domain of an immunoglobulin molecule has several beta strands that are arranged in two sheets. The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel. The CDRs are the loops that connect beta strands B-C, C'-C'', and F-G of the immunoglobulin fold, whereas the bottom loops that connect beta strands AB, CC', C'' -D and E-F of the immunoglobulin fold, and the top loop that connects the D-E strands of the immunoglobulin fold are the non-CDR loops. In some embodiments of this disclosure, at least some amino acid residues of a constant domain, CH1, CH2, or CH3, are part of the "non-CDR loop" of the binding moieties described herein. Non-CDR loops comprise, in some embodiments, one or more of AB, CD, EF, and DE loops of a C1-set domain of an Ig or an Ig-like molecule; AB, CC', EF, FG, BC, and EC' loops of a C2-set domain of an Ig or an Ig-like molecule; DE, BD, GF, A(A1A2)B, and EF loops of I(Intermediate)-set domain of an Ig or Ig-like molecule.

[78] Within the variable domain, the CDRs are believed to be responsible for antigen recognition and binding, while the FR residues are considered a scaffold for the CDRs. However, in certain cases, some of the FR residues play an important role in antigen recognition and binding. Framework region residues that affect Ag binding are divided into two categories. The first are FR residues that contact the antigen, thus are part of the binding-site, and some of these residues are close in sequence to the CDRs. Other residues are those that are far from the CDRs in sequence, but are in close proximity to it in the 3-D structure of the molecule, *e.g.*, a loop in heavy chain. The serum half-life extension domain (*e.g.*, a domain that comprises

CDRs) can comprise at least one non-CDR loop. In some embodiments, a non-CDR loop provides a binding site for binding to a cytokine, bulk serum protein or other target antigen.

[79] The serum half-life extension element, in addition to or alternatively to containing CDRs, comprises a non-CDR loop. In some embodiments, the non-CDR loop is modified to generate an antigen binding site specific for a desired target antigen, such as a bulk serum protein, such as albumin, or for the cytokine moiety or other targeting antigen. It is contemplated that various techniques can be used for modifying the non-CDR loop, e.g., site-directed mutagenesis, random mutagenesis, insertion of at least one amino acid that is foreign to the non-CDR loop amino acid sequence, amino acid substitution. An antigen peptide is inserted into a non-CDR loop, in some examples. In some examples, an antigenic peptide is substituted for the non-CDR loop. The modification, to generate an antigen binding site, is in some cases in only one non-CDR loop. In other instances, more than one non-CDR loop are modified. For instance, the modification is in any one of the non-CDR loops shown in **Fig. 5**, *i.e.*, AB, CC', C" D, EF, and D-E. In some cases, the modification is in the DE loop. In other cases the modifications are in all four of AB, CC', C" –D, E-F loops.

[80] In some examples, the serum half-life extension element has dual binding specificity and contains CDRs that specifically bind a bulk serum proteins, such as serum albumin, and non-CDR loops that specifically bind and block the cytokine domain. In other examples, the serum half-life extension element contains CDRs that specifically bind a target antigen, such as the cytokine domain or other target antigen, and non-CDR loops that specifically bind a bulk serum protein, such as serum albumin. Preferably, the serum half-life extension element inhibits binding of the cytokine domain to the cognate cytokine receptor, e.g. via steric occlusion, via specific intermolecular interactions, or a combination of both.

[81] In some embodiments, the serum half-life extension element noncovalently binds directly to the cytokine and inhibit its activity.

[82] In certain examples, the binding moiety binds to a cytokine via one or more of AB, CC', C" D, and E-F loop and binds to a bulk-serum protein, such as albumin, via one or more of BC, C'C", and FG loop. In certain examples, the binding moiety binds to a bulk serum protein, such as albumin, via its AB, CC', C" D, or EF loop and binds to a cytokine via its BC, C'C", or FG loop. In certain examples, the binding moiety of the binds to a bulk serum protein, such as albumin, via its AB, CC', C" D, and EF loop and is bound to a cytokine via its BC, C'C", and FG loop. In certain examples, the binding moiety binds to a bulk serum protein, such as albumin, via one or more of AB, CC', C" D, and E-F loop and binds to a cytokine, via one or more of BC, C'C", and FG loop.

[83] The binding moieties are any kinds of polypeptides. For example, in certain instances the binding moieties are natural peptides, synthetic peptides, or fibronectin scaffolds, or engineered bulk serum proteins. The bulk serum protein comprises, for example, albumin, fibrinogen, or a globulin. In some embodiments, the binding moieties are an engineered scaffolds. Engineered scaffolds comprise, for example, sdAb, a scFv, a Fab, a VHH, a fibronectin type III domain, immunoglobulin-like scaffold (as suggested in Halaby et al., 1999. Prot Eng 12(7):563-571), DARPIn, cystine knot peptide, lipocalin, three-helix bundle scaffold, protein G-related albumin-binding module, or a DNA or RNA aptamer scaffold.

[84] In some cases, the serum half-life extension element binds to the cytokine domain via its non-CDR loops and the cytokine domain is further connected to a targeting domain as described herein. In some cases, the serum half-life extending element comprises a binding site for a bulk serum protein. In some embodiments, the CDRs provide the binding site for the bulk serum protein. The bulk serum protein is, in some examples, a globulin, albumin, transferrin, IgG1, IgG2, IgG4, IgG3, IgA monomer, Factor XIII, Fibrinogen, IgE, or pentameric IgM. In some embodiments, the CDR form a binding site for an immunoglobulin light chain, such as an Igκ free light chain or an Igλ free light chain.

[85] One exemplary conditionally active protein is shown in **Fig. 6**. In the illustrated example, the non-CDR loops in a serum albumin binding domain (e.g. a dAb) can form a binding site for the cytokine IL-12. In this example, the binding site for serum albumin can be formed by the CDRs of the serum albumin binding domain.

[86] The serum half-life extension element can be any type of binding domain, including but not limited to, domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody. In some embodiments, the binding moiety is a single chain variable fragment (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody. In other embodiments, the binding moieties are non-Ig binding domains, i.e., antibody mimetic, such as anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPinS, fynomers, kunitz domain peptides, and monobodies.

[87] In other embodiments, the serum half-life extension element can be a water-soluble polymer or a peptide that is conjugated to a water-soluble polymer, such as PEG. “PEG,” “polyethylene glycol” and “poly(ethylene glycol)” as used herein, are interchangeable and encompass any nonpeptidic water-soluble poly(ethylene oxide). The term “PEG” also means a polymer that contains a majority, that is to say, greater than 50%, of —OCH₂CH₂— repeating subunits. With respect to specific forms, the PEG can take any number of a variety of molecular weights, as well as structures or geometries such as “branched,” “linear,” “forked,” “multifunctional,” and the like, to be described in greater detail below. The PEG is not limited to a particular structure and can be linear (e.g., an end capped, e.g., alkoxy PEG or a bifunctional PEG), branched or multi-armed (e.g., forked PEG or PEG attached to a polyol core), a dendritic (or star) architecture, each with or without one or more degradable linkages. Moreover, the internal structure of the PEG can be organized in any number of different repeat patterns and can be selected from the group consisting of homopolymer, alternating copolymer, random copolymer, block copolymer, alternating tripolymer, random tripolymer, and block tripolymer. PEGs can be conjugated to polypeptide and peptides through any suitable method. Typically a reactive PEG derivative, such as N-hydroxysuccinimidyl ester PEG, is reacted with a peptide or polypeptide that includes amino acids with a side chain that contains an amine, sulfhydryl, carboxylic acid or hydroxyl functional group, such as cysteine, lysine, asparagine, glutamine, theonine, tyrosine, serine, aspartic acid, and glutamic acid.

Targeting and Retention Domains

[88] For certain applications, it may be desirable to maximize the amount of time the construct is present in its desired location in the body. This can be achieved by including one further domain in the chimeric polypeptide (fusion protein) to influence its movements within the body. For example, the chimeric nucleic acids can encode a domain that directs the polypeptide to a location in the body, e.g., tumor cells or a site of inflammation; this domain is termed a “targeting domain” and/or encode a domain that retains the polypeptide in a location in the body, e.g., tumor cells or a site of inflammation; this domain is termed a “retention domain”. In some embodiments a domain can function as both a targeting and a retention domain. In some embodiments, the targeting domain and/or retention domain are specific to a protease-rich environment. In some embodiments, the encoded targeting domain and/or retention domain are specific for regulatory T cells (Tregs), for example targeting the CCR4 or CD39 receptors. Other suitable targeting and/or retention domains comprise those that have a cognate ligand that is overexpressed in inflamed tissues, e.g., the IL-1 receptor, or the IL-6 receptor. In other embodiments, the suitable targeting and/or retention domains comprise those who have a cognate ligand that is overexpressed in tumor tissue, e.g., Epcam, CEA or mesothelin. In some embodiments, the targeting domain is linked to the interleukin via a linker which is cleaved at the site of action (e.g. by inflammation or cancer specific proteases) releasing the interleukin full activity at the desired site. In some embodiments, the targeting and/or retention domain is linked to the interleukin via a linker which is not cleaved at the site of action (e.g. by inflammation or cancer specific proteases), causing the cytokine to remain at the desired site.

[89] Antigens of choice, in some cases, are expressed on the surface of a diseased cell or tissue, for example a tumor or a cancer cell. Antigens useful for tumor targeting and retention include but are not limited to Fibroblast activation protein alpha (FAPa), Trophoblast glycoprotein (ST4), Tumor-associated calcium signal transducer 2 (Trop2), Fibronectin EDB (EDB-FN), FOLR1, fibronectin EIIIB domain, EpCAM, EGFR, HER-2, HER-3, c-Met, FOLR1, and CEA. Pharmaceutical compositions disclosed herein, also include proteins comprising two targeting and/or retention domains that bind to two different target antigens known to be expressed on a diseased cell or tissue. Exemplary pairs of antigen binding domains include but are not limited to EGFR/CEA, EpCAM/CEA, and HER-2/HER-3.

[90] Suitable targeting and/or retention domains include antigen-binding domains, such as antibodies and fragments thereof including, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody a single chain variable fragment (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain of camelid-type nanobody (VHH), a dAb and the like. Other suitable antigen-binding domain include non-immunoglobulin proteins that mimic antibody binding and/or structure such as, anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPins, fynomers, kunitz domain peptides, monobodies, and binding domains based on other engineered scaffolds such as SpA,

GroEL, fibronectin, lipocalin and CTLA4 scaffolds. Further examples of antigen-binding polypeptides include a ligand for a desired receptor, a ligand-binding portion of a receptor, a lectin, and peptides that binds to or associates with one or more target antigens.

[91] In some embodiments, the targeting and/or retention domains specifically bind to a cell surface molecule. In some embodiments, the targeting and/or retention domains specifically bind to a tumor antigen. In some embodiments, the targeting polypeptides specifically and independently bind to a tumor antigen selected from at least one of Fibroblast activation protein alpha (FAPa), Trophoblast glycoprotein (5T4), Tumor-associated calcium signal transducer 2 (Trop2), Fibronectin EDB (EDB-FN), FOLR1, fibronectin EIIIB domain, EpCAM, EGFR, HER-2, HER-3, cMet, CEA, and FOLR1. In some embodiments, the targeting polypeptides specifically and independently bind to two different antigens, wherein at least one of the antigens is a tumor antigen selected from Fibroblast activation protein alpha (FAPa), Trophoblast glycoprotein (5T4), Tumor-associated calcium signal transducer 2 (Trop2), Fibronectin EDB (EDB-FN), FOLR1, fibronectin EIIIB domain, EpCAM, EGFR, HER-2, HER-3, cMet, CEA, and FOLR1.

[92] The targeting and/or retention antigen can be a tumor antigen expressed on a tumor cell. Tumor antigens are well known in the art and include, for example, Fibroblast activation protein alpha (FAPa), Trophoblast glycoprotein (5T4), Tumor-associated calcium signal transducer 2 (Trop2), Fibronectin EDB (EDB-FN), FOLR1, fibronectin EIIIB domain, EpCAM, EGFR, HER-2, HER-3, c-Met, FOLR1, PSMA, CD38, BCMA, and CEA. 5T4, AFP, B7-H3, Cadherin-6, CAIX, CD117, CD123, CD138, CD166, CD19, CD20, CD205, CD22, CD30, CD33, CD352, CD37, CD44, CD52, CD56, CD70, CD71, CD74, CD79b, DLL3, EphA2, FAP, FGFR2, FGFR3, GPC3, gpA33, FLT-3, gpNMB, HPV-16 E6, HPV-16 E7, ITGA2, ITGA3, SLC39A6, MAGE, mesothelin, Muc1, Muc16, NaPi2b, Nectin-4, P-cadherin, NY-ESO-1, PRLR, PSCA, PTK7, ROR1, SLC44A4, SLTRK5, SLTRK6, STEAP1, TIM1, Trop2, WT1.

[93] The targeting and/or retention antigen can be an immune checkpoint protein. Examples of immune checkpoint proteins include but are not limited to CD27, CD137, 2B4, TIGIT, CD155, ICOS, HVEM, CD40L, LIGHT, TIM-1, OX40, DNAM-1, PD-L1, PD1, PD-L2, CTLA-4, CD8, CD40, CEACAM1, CD48, CD70, A2AR, CD39, CD73, B7-H3, B7-H4, BTLA, IDO1, IDO2, TDO, KIR, LAG-3, TIM-3, or VISTA.

[94] The targeting and/or retention antigen can be a cell surface molecule such as a protein, lipid or polysaccharide. In some embodiments, a targeting and/or retention antigen is a on a tumor cell, virally infected cell, bacterially infected cell, damaged red blood cell, arterial plaque cell, inflamed or fibrotic tissue cell. The targeting and/or retention antigen can comprise an immune response modulator. Examples of immune response modulator include but are not limited to granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 12 (IL-12), interleukin 15 (IL-15), B7-1 (CD80), B7-2 (CD86), GITRL, CD3, or GITR.

[95] The targeting and/or retention antigen can be a cytokine receptor. Examples, of cytokine receptors include but are not limited to Type I cytokine receptors, such as GM-CSF receptor, G-CSF receptor, Type I

IL receptors, Epo receptor, LIF receptor, CNTF receptor, TPO receptor; Type II Cytokine receptors, such as IFN-alpha receptor (IFNAR1, IFNAR2), IFN-beta receptor, IFN-gamma receptor (IFNGR1, IFNGR2), Type II IL receptors; chemokine receptors, such as CC chemokine receptors, CXC chemokine receptors, CX3C chemokine receptors, XC chemokine receptors; tumor necrosis receptor superfamily receptors, such as TNFRSF5/CD40, TNFRSF8/CD30, TNFRSF7/CD27, TNFRSF1A/TNFR1/CD120a, TNFRSF1B / TNFR2 / CD120b; TGF-beta receptors, such as TGF-beta receptor 1, TGF-beta receptor 2; Ig super family receptors, such as IL-1 receptors, CSF-1R, PDGFR (PDGFRA, PDGFRB), SCFR.

Linkers

[96] As stated above, the pharmaceutical compositions comprise one or more linker sequences. A linker sequence serves to provide flexibility between polypeptides, such that, for example, the blocking moiety is capable of inhibiting the activity of the cytokine polypeptide. The linker sequence can be located between any or all of the cytokine polypeptide, the serum half-life extension element, and/or the blocking moiety. As described herein at least one of the linkers is protease cleavable, and contains a (one or more) cleavage site for a (one or more) desired protease. Preferably, the desired protease is enriched or selectively expressed at the desired site of cytokine activity (e.g., the tumor microenvironment). Thus, the fusion protein is preferentially or selectively cleaved at the site of desired cytokine activity.

[97] The orientation of the components of the pharmaceutical composition, are largely a matter of design choice and it is recognized that multiple orientations are possible and all are intended to be encompassed by this disclosure. For example, a blocking moiety can be located C-terminally or N-terminally to a cytokine polypeptide.

[98] Proteases known to be associated with diseased cells or tissues include but are not limited to serine proteases, cysteine proteases, aspartate proteases, threonine proteases, glutamic acid proteases, metalloproteases, asparagine peptide lyases, serum proteases, cathepsins, Cathepsin B, Cathepsin C, Cathepsin D, Cathepsin E, Cathepsin K, Cathepsin L, kallikreins, hK1, hK10, hK15, plasmin, collagenase, Type IV collagenase, stromelysin, Factor Xa, chymotrypsin-like protease, trypsin-like protease, elastase-like protease, subtilisin-like protease, actinidain, bromelain, calpain, caspases, caspase-3, Mirt-CP, papain, HIV-1 protease, HSV protease, CMV protease, chymosin, renin, pepsin, matriptase, legumain, plasmepsin, nepenthesin, metalloexopeptidases, metalloendopeptidases, matrix metalloproteases (MMP), MMP1, MMP2, MMP3, MMP8, MMP9, MMP13, MMP11, MMP14, urokinase plasminogen activator (uPA), enterokinase, prostate-specific antigen (PSA, hK3), interleukin-1 β converting enzyme, thrombin, FAP (FAP-a), dipeptidyl peptidase, neprins, granzymes and dipeptidyl peptidase IV (DPPIV/CD26). Proteases capable of cleaving amino acid sequences encoded by the chimeric nucleic acid sequences provided herein can, for example, be selected from the group consisting of a prostate specific antigen (PSA), a matrix metalloproteinase (MMP), an ADAM, a Disintegrin and a Metalloproteinase (ADAM), a plasminogen activator, a cathepsin, a caspase, a tumor

cell surface protease, and an elastase. The MMP can, for example, be matrix metalloproteinase 2 (MMP2) or matrix metalloproteinase 9 (MMP9).

[99] Proteases useful in the methods disclosed herein are presented in Table 1, and exemplary proteases and their cleavage site are presented in Table 1a:

Table 1. Proteases relevant to inflammation and cancer

Protease	Specificity	Other aspects
<i>Secreted by killer T cells:</i>		
Granzyme B (grB)	Cleaves after Asp residues (asp-ase)	Type of serine protease; strongly implicated in inducing perforin-dependent target cell apoptosis
Granzyme A (grA)	trypsin-like, cleaves after basic residues	Type of serine protease;
Granzyme H (grH)	Unknown substrate specificity	Type of serine protease; <i>Other granzymes are also secreted by killer T cells, but not all are present in humans</i>
Caspase-8	Cleaves after Asp residues	Type of cysteine protease; plays essential role in TCR-induced cellular expansion-exact molecular role unclear
Mucosa-associated lymphoid tissue (MALT1)	Cleaves after arginine residues	Type of cysteine protease; likely acts both as a scaffold and proteolytically active enzyme in the CBM-dependent signaling pathway
Tryptase	Targets: angiotensin I, fibrinogen, prourokinase, TGF β ; preferentially cleaves proteins after lysine or arginine residues	Type of mast cell-specific serine protease; trypsin-like; resistant to inhibition by macromolecular protease inhibitors expressed in mammals due to their tetrameric structure, with all sites facing narrow central pore; <i>also associated with inflammation</i>
<i>Associated with inflammation:</i>		
Thrombin	Targets: FGF-2, HB-EGF, Osteo-pontin, PDGF, VEGF	Type of serine protease; modulates activity of vascular growth factors, chemokines and extracellular proteins; strengthens VEGF-induced proliferation; induces cell migration; angiogenic factor; regulates hemostasis
Chymase	Exhibit chymotrypsin-like specificity, cleaving proteins after aromatic amino acid residues	Type of mast cell-specific serine protease
Carboxypeptidase A (MC-CPA)	Cleaves amino acid residues from C-terminal	Type of zinc-dependent metalloproteinase

	end of peptides and proteins	
Kallikreins	Targets: high molecular weight kininogen, pro-urokinase	Type of serine protease; modulate relaxation response; contribute to inflammatory response; fibrin degradation
Elastase	Targets: E-cadherin, GM-CSF, IL-1, IL-2, IL-6, IL-8, p38 ^{MAPK} , TNF α , VE-cadherin	Type of neutrophil serine protease; degrades ECM components; regulates inflammatory response; activates pro-apoptotic signaling
Cathepsin G	Targets: EGF, ENA-78, IL-8, MCP-1, MMP-2, MT1-MMP, PAI-1, RANTES, TGF β , TNF α	Type of serine protease; degrades ECM components; chemo-attractant of leukocytes; regulates inflammatory response; promotes apoptosis
PR-3	Targets: ENA-78, IL-8, IL-18, JNK, p38 ^{MAPK} , TNF α	Type of serine protease; promotes inflammatory response; activates pro-apoptotic signaling
Granzyme M (grM)	Cleaves after Met and other long, unbranched hydrophobic residues	Type of serine protease; only expressed in NK cells
Calpains	Cleave between Arg and Gly	Family of cysteine proteases; calcium-dependent; activation is involved in the process of numerous inflammation-associated diseases

Table 1a: Exemplary Proteases and Protease Recognition Sequences

Protease	Cleavage Domain Sequence	SEQ ID NO:
MMP7	KRALGLPG	2
MMP7	(DE) ₈ RPLALWRS(DR) ₈	3
MMP9	PR(S/T)(L/I)(S/T)	4
MMP9	LEATA	5
MMP11	GGAANLVRGG	6

MMP14	SGRIGFLRTA	7
MMP	PLGLAG	8
MMP	PLGLAX	9
MMP	PLGC(me)AG	10
MMP	ESPAYYTA	11
MMP	RLQLKL	12
MMP	RLQLKAC	13
MMP2, MMP9, MMP14	EP(Cit)G(Hof)YL	14
Urokinase plasminogen activator (uPA)	SGRSA	15
Urokinase plasminogen activator (uPA)	DAFK	16
Urokinase plasminogen activator (uPA)	GGGRR	17
Lysosomal Enzyme	GFLG	18
Lysosomal Enzyme	ALAL	19
Lysosomal Enzyme	FK	20
Cathepsin B	NLL	21
Cathepsin D	PIC(Et)FF	22

Cathepsin K	GGPRGLPG	23
Prostate Specific Antigen	HSSKLQ	24
Prostate Specific Antigen	HSSKLQL	25
Prostate Specific Antigen	HSSKLQEDA	26
Herpes Simplex Virus Protease	LVLASSSFGY	27
HIV Protease	GVSQNYPIVG	28
CMV Protease	GVVQASCRLA	29
Thrombin	F(Pip)RS	30
Thrombin	DPRSFL	31
Thrombin	PPRSFL	32
Caspase-3	DEV D	33
Caspase-3	DEVDP	34
Caspase-3	KGSGDVEG	35
Interleukin 1β converting enzyme	GWEHDG	36
Enterokinase	EDDDDKA	37
FAP	KQEQNPGST	38

Kallikrein 2	GKAFRR	39
Plasmin	DAFK	40
Plasmin	DVLK	41
Plasmin	DAFK	42
TOP	ALLLALL	43

[100] Provided herein are pharmaceutical compositions comprising polypeptide sequences. As with all peptides, polypeptides, and proteins, including fragments thereof, it is understood that additional modifications in the amino acid sequence of the chimeric polypeptides (amino acid sequence variants) can occur that do not alter the nature or function of the peptides, polypeptides, or proteins. Such modifications include conservative amino acid substitutions and are discussed in greater detail below.

[101] The compositions provided herein have a desired function. The compositions are comprised of at least an IL-12 cytokine polypeptide, a blocking moiety, e.g. a steric blocking polypeptide, and an optional serum half-life extension element, and an optional targeting polypeptide, with one or more linkers connecting each polypeptide in the composition. The first polypeptide, e.g., an IL-12 polypeptide, is provided to be an active agent. The blocking moiety is provided to block the activity of the interleukin. The linker polypeptide, e.g., a protease cleavable polypeptide, is provided to be cleaved by a protease that is specifically expressed at the intended target of the active agent. Optionally, the blocking moiety blocks the activity of the first polypeptide by binding the interleukin polypeptide. In some embodiments, the blocking moiety, e.g. a steric blocking peptide, is linked to the interleukin via a protease-cleavable linker which is cleaved at the site of action (e.g. by inflammation specific proteases) releasing the cytokine full activity at the desired site.

[102] The protease cleavage site may be a naturally occurring protease cleavage site or an artificially engineered protease cleavage site. The artificially engineered protease cleavage site can be cleaved by more than one protease specific to the desired environment in which cleavage will occur, e.g. a tumor. The protease cleavage site may be cleavable by at least one protease, at least two proteases, at least three proteases, or at least four proteases.

[103] In some embodiments, the linker comprises glycine-glycine, a sortase-recognition motif, or a sortase-recognition motif and a peptide sequence (Gly₄Ser)_n (SEQ ID NO: 81) or (Gly₃Ser)_n (SEQ ID NO: 82), wherein n is 1, 2, 3, 4 or 5. In one embodiment, the sortase-recognition motif comprises a

peptide sequence LPXTG (SEQ ID NO: 80), where X is any amino acid. In one embodiment, the covalent linkage is between a reactive lysine residue attached to the C-terminal of the cytokine polypeptide and a reactive aspartic acid attached to the N-terminal of the blocking or other moiety. In one embodiment, the covalent linkage is between a reactive aspartic acid residue attached to the N-terminal of the cytokine polypeptide and a reactive lysine residue attached to the C-terminal of the blocking or other moiety.

Cleavage and Inducibility

[104] As described herein, the activity of the cytokine polypeptide in the context of the fusion protein is attenuated, and protease cleavage at the desired site of activity, such as in a tumor microenvironment, releases a form of the cytokine from the fusion protein that is much more active as a cytokine receptor agonist than the fusion protein. For example, the cytokine-receptor activating (agonist) activity of the fusion polypeptide can be at least about 10X, at least about 50X, at least about 100X, at least about 250X, at least about 500X, or at least about 1000x less than the cytokine receptor activating activity of the cytokine polypeptide as a separate molecular entity. The cytokine polypeptide that is part of the fusion protein exists as a separate molecular entity when it contains an amino acid that is substantially identical to the cytokine polypeptide and does not substantially include additional amino acids and is not associated (by covalent or non-covalent bonds) with other molecules. If necessary, a cytokine polypeptide as a separate molecular entity may include some additional amino acid sequences, such as a tag or short sequence to aid in expression and/or purification.

[105] In other examples, the cytokine-receptor activating (agonist) activity of the fusion polypeptide is at least about 10X, at least about 50X, at least about 100X, at least about 250X, at least about 500X, or about 1000x less than the cytokine receptor activating activity of the polypeptide that contains the cytokine polypeptide that is produced by cleavage of the protease cleavable linker in the fusion protein. In other words, the cytokine receptor activating (agonist) activity of the polypeptide that contains the cytokine polypeptide that is produced by cleavage of the protease cleavable linker in the fusion protein is at least about 10X, at least about 50X, at least about 100X, at least about 250X, at least about 500X, or at least about 1000x greater than the cytokine receptor activating activity of the fusion protein.

Polypeptide substitutions

[106] The polypeptides described herein can include components (e.g., the cytokine, the blocking moiety) that have the same amino acid sequence of the corresponding naturally occurring protein (e.g., IL-2, IL-15, HSA) or can have an amino acid sequence that differs from the naturally occurring protein so long as the desired function is maintained. It is understood that one way to define any known modifications and derivatives or those that might arise, of the disclosed proteins and nucleic

acids that encode them is through defining the sequence variants in terms of identity to specific known reference sequences. Specifically disclosed are polypeptides and nucleic acids which have at least, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 percent identity to the chimeric polypeptides provided herein. For example, provided are polypeptides or nucleic acids that have at least, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 percent identity to the sequence of any of the nucleic acids or polypeptides described herein. Those of skill in the art readily understand how to determine the identity of two polypeptides or two nucleic acids. For example, the identity can be calculated after aligning the two sequences so that the identity is at its highest level.

[107] Another way of calculating identity can be performed by published algorithms. Optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman Adv. Appl. Math. 2:482 (1981), by the identity alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by inspection.

[108] The same types of identity can be obtained for nucleic acids by, for example, the algorithms disclosed in Zuker, Science 244:48-52 (1989); Jaeger et al., Proc. Natl. Acad. Sci. USA 86:7706-7710 (1989); Jaeger et al., Methods Enzymol. 183:281-306 (1989), which are herein incorporated by reference for at least material related to nucleic acid alignment. It is understood that any of the methods typically can be used and that in certain instances the results of these various methods may differ, but the skilled artisan understands if identity is found with at least one of these methods, the sequences would be said to have the stated identity, and be disclosed herein.

[109] Protein modifications include amino acid sequence modifications. Modifications in amino acid sequence may arise naturally as allelic variations (e.g., due to genetic polymorphism), may arise due to environmental influence (e.g., by exposure to ultraviolet light), or may be produced by human intervention (e.g., by mutagenesis of cloned DNA sequences), such as induced point, deletion, insertion and substitution mutants. These modifications can result in changes in the amino acid sequence, provide silent mutations, modify a restriction site, or provide other specific mutations. Amino acid sequence modifications typically fall into one or more of three classes: substitutional, insertional or deletional modifications. Insertions include amino and/or carboxyl terminal fusions as well as intrasequence insertions of single or multiple amino acid residues. Insertions ordinarily will be smaller insertions than those of amino or carboxyl terminal fusions, for example, on the order of one to four residues. Deletions are characterized by the removal of one or more amino acid residues from the protein sequence. Typically, no more than about from 2 to 6 residues are deleted at any one site within the protein molecule. Amino acid substitutions are typically of single residues, but can occur at a number of different locations at once; insertions usually will be on the order of about from 1 to 10

amino acid residues; and deletions will range about from 1 to 30 residues. Deletions or insertions preferably are made in adjacent pairs, i.e. a deletion of 2 residues or insertion of 2 residues. Substitutions, deletions, insertions or any combination thereof may be combined to arrive at a final construct. The mutations must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure. Substitutional modifications are those in which at least one residue has been removed and a different residue inserted in its place. Such substitutions generally are made in accordance with the following Table 2 and are referred to as conservative substitutions.

Table 2. Exemplary amino acid substitutions

Amino Acid	Exemplary Substitutions
Ala	Ser, Gly, Cys
Arg	Lys, Gln, Met, Ile
Asn	Gln, His, Glu, Asp
Asp	Glu, Asn, Gln
Cys	Ser, Met, Thr
Gln	Asn, Lys, Glu, Asp
Glu	Asp, Asn, Gln
Gly	Pro, Ala
His	Asn, Gln
Ile	Leu, Val, Met
Leu	Ile, Val, Met
Lys	Arg, Gln, Met, Ile
Met	Leu, Ile, Val
Phe	Met, Leu, Tyr, Trp, His

Ser	Thr, Met, Cys
Thr	Ser, Met, Val
Trp	Tyr, Phe
Tyr	Trp, Phe, His
Val	Ile, Leu, Met

[110] Modifications, including the specific amino acid substitutions, are made by known methods. For example, modifications are made by site specific mutagenesis of nucleotides in the DNA encoding the polypeptide, thereby producing DNA encoding the modification, and thereafter expressing the DNA in recombinant cell culture. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example M13 primer mutagenesis and PCR mutagenesis.

[111] Modifications can be selected to optimize binding. For example, affinity maturation techniques can be used to alter binding of the scFv by introducing random mutations inside the complementarity determining regions (CDRs). Such random mutations can be introduced using a variety of techniques, including radiation, chemical mutagens or error-prone PCR. Multiple rounds of mutation and selection can be performed using, for example, phage display.

[112] The disclosure also relates to nucleic acids that encode the chimeric polypeptides described herein, and to the use of such nucleic acids to produce the chimeric polypeptides and for therapeutic purposes. For example, the invention includes DNA and RNA molecules (e.g., mRNA, self-replicating RNA) that encode a chimeric polypeptide and to the therapeutic use of such DNA and RNA molecules.

Exemplary Compositions

[113] Exemplary fusion proteins of the invention combine the above described elements in a variety of orientations. The orientations described in this section are meant as examples and are not to be considered limiting.

[114] In some embodiments, the fusion protein comprises an IL-12 polypeptide, a blocking moiety and a half-life extension element. In some embodiments, the IL-12 polypeptide, is positioned between the half-life extension element and the blocking moiety. In some embodiments, the IL-12 polypeptide, is N-terminal to the blocking moiety and the half-life extension element. In some such embodiments, IL-12 polypeptide, is proximal to the blocking moiety; in some such embodiments, the IL-12 polypeptide, is proximal to the half-life extension element. At least one protease-cleavable linker must be included in all embodiments, such that the IL-12 polypeptide, may be active upon cleavage. In some embodiments, the IL-12 polypeptide, is C-terminal to the blocking moiety and the

half-life extension element. Additional elements may be attached to one another by a cleavable linker, a non-cleavable linker, or by direct fusion.

[115] In some embodiments, the blocking domains used are capable of extending half-life, and the IL-12 polypeptide, is positioned between two such blocking domains. In some embodiments, the IL-12 polypeptide, is positioned between two blocking domains, one of which is capable of extending half-life.

[116] In some embodiments, two cytokines are included in the same construct. In some embodiments, the cytokines are connected to two blocking domains each (three in total in one molecule), with a blocking domain between the two cytokine domains. In some embodiments, one or more additional half-life extension domains may be included to optimize pharmacokinetic properties.

[117] In some embodiments, three cytokines are included in the same construct. In some embodiments, the third cytokine may function to block the other two in place of a blocking domain between the two cytokines.

[118] Preferred half-life extension elements for use in the fusion proteins are human serum albumin (HSA), an antibody or antibody fragment (e.g., scFV, dAb) which binds serum albumin, a human or humanized IgG, or a fragment of any of the foregoing. In some preferred embodiments, the blocking moiety is human serum albumin (HSA), or an antibody or antibody fragment which binds serum albumin, an antibody which binds the cytokine and prevents activation of binding or activation of the cytokine receptor, another cytokine, or a fragment of any of the foregoing. In preferred embodiments comprising an additional targeting domain, the targeting domain is an antibody which binds a cell surface protein which is enriched on the surface of cancer cells, such as EpCAM, FOLR1, and Fibronectin.

Methods of treatment and Pharmaceutical Compositions

[119] Further provided are methods of treating a subject with or at risk of developing an of a disease or disorder, such as proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, a viral disease, an allergic reaction, a parasitic reaction, or graft-versus-host disease. The methods administering to a subject in need thereof an effective amount of a fusion protein as disclosed herein that is typically administered as a pharmaceutical composition. In some embodiments, the method further comprises selecting a subject with or at risk of developing such a disease or disorder. The pharmaceutical composition preferably comprises a blocked IL-12 polypeptide, fragment or mutein thereof that is activated at a site of inflammation. In one embodiment, the chimeric polypeptide comprises an IL-12 polypeptide, fragment or mutein thereof and a serum half-life extension element. In another embodiment, the chimeric polypeptide comprises an IL-12 polypeptide, fragment or mutein thereof and a blocking moiety, e.g. a steric blocking polypeptide, wherein the steric blocking polypeptide is capable of sterically blocking the activity of the IL-12 polypeptide, fragment or mutein thereof. In another embodiment, the chimeric polypeptide comprises an IL-12 polypeptide, fragment or mutein thereof, a

blocking moiety, and a serum half-life extension element.

[120] Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, and is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. Inflammation can occur from infection, as a symptom or a disease, e.g., cancer, atherosclerosis, allergies, myopathies, HIV, obesity, or an autoimmune disease. An autoimmune disease is a chronic condition arising from an abnormal immune response to a self-antigen. Autoimmune diseases that may be treated with the polypeptides disclosed herein include but are not limited to lupus, celiac disease, diabetes mellitus type 1, Graves disease, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.

[121] The pharmaceutical composition can comprise one or more protease-cleavable linker sequences. The linker sequence serves to provide flexibility between polypeptides, such that each polypeptide is capable of inhibiting the activity of the first polypeptide. The linker sequence can be located between any or all of the cytokine polypeptide, fragment or mutein thereof, the blocking moiety, and serum half-life extension element. Optionally, the composition comprises, two, three, four, or five linker sequences. The linker sequence, two, three, or four linker sequences can be the same or different linker sequences. In one embodiment, the linker sequence comprises GGGGS (SEQ ID NO: 87), GSGSGS (SEQ ID NO: 88), or G(SGGG)₂SGGT (SEQ ID NO: 89). In another embodiment, the linker comprises a protease-cleavable sequence selected from group consisting of HSKLQ (SEQ ID NO: 24), GPLGVRG (SEQ ID NO: 83), IPVSLRSG (SEQ ID NO: 84), VPLSLYSG (SEQ ID NO: 85), and SGESPAYTA (SEQ ID NO: 86).

[122] Suitable linkers can be of different lengths, such as from 1 amino acid (e.g., Gly) to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids, and may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids.

[123] In some embodiments, the linker is cleaved by a protease selected from the group consisting of a kallikrein, thrombin, chymase, carboxypeptidase A, cathepsin G, an elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), a plasminogen activator, a cathepsin, a caspase, a tryptase, or a tumor cell surface protease.

[124] Further provided are methods of treating a subject with or at risk of developing cancer. The methods comprise administering to the subject in need thereof an effective amount of a chimeric polypeptide (a fusion protein) as disclosed herein that is typically administered as a pharmaceutical composition. In some embodiments, the method further comprises selecting a subject with or at risk of

developing cancer. The pharmaceutical composition preferably comprises a blocked cytokine, fragment or mutein thereof that is activated at a tumor site. Preferably, the tumor is a solid tumor. The cancer may be a colon cancer, a lung cancer, a melanoma, a sarcoma, a renal cell carcinoma, a breast cancer...

[125] The method can further involve the administration of one or more additional agents to treat cancer, such as chemotherapeutic agents (e.g., Adriamycin, Cerubidine, Bleomycin, Alkeran, Velban, Oncovin, Fluorouracil, Thiotepa, Methotrexate, Bisantrene, Noantrone, Thiguanine, Cytaribine, Procarabazine), immuno-oncology agents (e.g., anti-PD-L1, anti-CTLA4, anti-PD-1, anti-CD47, anti-GD2), cellular therapies (e.g., CAR-T, T-cell therapy), oncolytic viruses and the like.

[126] Provided herein are pharmaceutical formulations or compositions containing the chimeric polypeptides and a pharmaceutically acceptable carrier. The herein provided compositions are suitable for administration *in vitro* or *in vivo*. By pharmaceutically acceptable carrier is meant a material that is not biologically or otherwise undesirable, i.e., the material is administered to a subject without causing undesirable biological effects or interacting in a deleterious manner with the other components of the pharmaceutical formulation or composition in which it is contained. The carrier is selected to minimize degradation of the active ingredient and to minimize adverse side effects in the subject.

[127] Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy*, 21st Edition, David B. Troy, ed., Lippicott Williams & Wilkins (2005). Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic, although the formulate can be hypertonic or hypotonic if desired. Examples of the pharmaceutically-acceptable carriers include, but are not limited to, sterile water, saline, buffered solutions like Ringer's solution, and dextrose solution. The pH of the solution is generally about 5 to about 8 or from about 7 to 7.5. Other carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the immunogenic polypeptides. Matrices are in the form of shaped articles, e.g., films, liposomes, or microparticles. Certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of composition being administered. Carriers are those suitable for administration of the chimeric polypeptides or nucleic acid sequences encoding the chimeric polypeptides to humans or other subjects.

[128] The pharmaceutical formulations or compositions are administered in a number of ways depending on whether local or systemic treatment is desired and on the area to be treated. The compositions are administered via any of several routes of administration, including topically, orally, parenterally, intravenously, intra-articularly, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally, intrahepatically, intracranially, nebulization/inhalation, or by installation via bronchoscopy. In some embodiments, the compositions are administered locally (non-systemically), including intratumorally, intra-articularly, intrathecally, etc.

[129] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives are optionally present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

[130] Formulations for topical administration include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder, or oily bases, thickeners and the like are optionally necessary or desirable.

[131] Compositions for oral administration include powders or granules, suspension or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders are optionally desirable.

[132] Optionally, the chimeric polypeptides or nucleic acid sequences encoding the chimeric polypeptides are administered by a vector. There are a number of compositions and methods which can be used to deliver the nucleic acid molecules and/or polypeptides to cells, either *in vitro* or *in vivo* via, for example, expression vectors. These methods and compositions can largely be broken down into two classes: viral based delivery systems and non-viral based delivery systems. Such methods are well known in the art and readily adaptable for use with the compositions and methods described herein. Such compositions and methods can be used to transfect or transduce cells *in vitro* or *in vivo*, for example, to produce cell lines that express and preferably secrete the encoded chimeric polypeptide or to therapeutically deliver nucleic acids to a subject. The components of the chimeric nucleic acids disclosed herein typically are operably linked in frame to encode a fusion protein.

[133] As used herein, plasmid or viral vectors are agents that transport the disclosed nucleic acids into the cell without degradation and include a promoter yielding expression of the nucleic acid molecule and/or polypeptide in the cells into which it is delivered. Viral vectors are, for example, Adenovirus, Adeno-associated virus, herpes virus, Vaccinia virus, Polio virus, Sindbis, and other RNA viruses, including these viruses with the HIV backbone. Also preferred are any viral families which share the properties of these viruses which make them suitable for use as vectors. Retroviral vectors, in general are described by Coffin et al., *Retroviruses*, Cold Spring Harbor Laboratory Press (1997), which is incorporated by reference herein for the vectors and methods of making them. The construction of replication-defective adenoviruses has been described (Berkner et al., *J. Virol.* 61:1213-20 (1987); Massie et al., *Mol. Cell. Biol.* 6:2872-83 (1986); Haj-Ahmad et al., *J. Virol.* 57:267-74 (1986); Davidson et al., *J. Virol.* 61:1226-39 (1987); Zhang et al., *BioTechniques* 15:868-72 (1993)). The benefit and the use of these viruses as vectors is that they are limited in the extent to

which they can spread to other cell types, since they can replicate within an initial infected cell, but are unable to form new infectious viral particles. Recombinant adenoviruses have been shown to achieve high efficiency after direct, in vivo delivery to airway epithelium, hepatocytes, vascular endothelium, CNS parenchyma, and a number of other tissue sites. Other useful systems include, for example, replicating and host-restricted non-replicating vaccinia virus vectors.

[134] The provided polypeptides and/or nucleic acid molecules can be delivered via virus like particles. Virus like particles (VLPs) consist of viral protein(s) derived from the structural proteins of a virus. Methods for making and using virus like particles are described in, for example, Garcea and Gissmann, *Current Opinion in Biotechnology* 15:513-7 (2004).

[135] The provided polypeptides can be delivered by subviral dense bodies (DBs). DBs transport proteins into target cells by membrane fusion. Methods for making and using DBs are described in, for example, Pepperl-Klindworth et al., *Gene Therapy* 10:278-84 (2003).

[136] The provided polypeptides can be delivered by tegument aggregates. Methods for making and using tegument aggregates are described in International Publication No. WO 2006/110728.

[137] Non-viral based delivery methods, can include expression vectors comprising nucleic acid molecules and nucleic acid sequences encoding polypeptides, wherein the nucleic acids are operably linked to an expression control sequence. Suitable vector backbones include, for example, those routinely used in the art such as plasmids, artificial chromosomes, BACs, YACs, or PACs. Numerous vectors and expression systems are commercially available from such corporations as Novagen (Madison, Wis.), Clontech (Pal Alto, Calif.), Stratagene (La Jolla, Calif.), and Invitrogen/Life Technologies (Carlsbad, Calif.). Vectors typically contain one or more regulatory regions. Regulatory regions include, without limitation, promoter sequences, enhancer sequences, response elements, protein recognition sites, inducible elements, protein binding sequences, 5' and 3' untranslated regions (UTRs), transcriptional start sites, termination sequences, polyadenylation sequences, and introns. Such vectors can also be used to make the chimeric polypeptides by expression in a suitable host cell, such as CHO cells.

[138] Preferred promoters controlling transcription from vectors in mammalian host cells may be obtained from various sources, for example, the genomes of viruses such as polyoma, Simian Virus 40 (SV40), adenovirus, retroviruses, hepatitis B virus, and most preferably cytomegalovirus (CMV), or from heterologous mammalian promoters, e.g. β -actin promoter or EF1 α promoter, or from hybrid or chimeric promoters (e.g., CMV promoter fused to the β -actin promoter). Of course, promoters from the host cell or related species are also useful herein.

[139] Enhancer generally refers to a sequence of DNA that functions at no fixed distance from the transcription start site and can be either 5' or 3' to the transcription unit. Furthermore, enhancers can be within an intron as well as within the coding sequence itself. They are usually between 10 and 300 base pairs (bp) in length, and they function in cis. Enhancers usually function to increase transcription from nearby promoters. Enhancers can also contain response elements that mediate the regulation of

transcription. While many enhancer sequences are known from mammalian genes (globin, elastase, albumin, fetoprotein, and insulin), typically one will use an enhancer from a eukaryotic cell virus for general expression. Preferred examples are the SV40 enhancer on the late side of the replication origin, the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

[140] The promoter and/or the enhancer can be inducible (e.g. chemically or physically regulated). A chemically regulated promoter and/or enhancer can, for example, be regulated by the presence of alcohol, tetracycline, a steroid, or a metal. A physically regulated promoter and/or enhancer can, for example, be regulated by environmental factors, such as temperature and light. Optionally, the promoter and/or enhancer region can act as a constitutive promoter and/or enhancer to maximize the expression of the region of the transcription unit to be transcribed. In certain vectors, the promoter and/or enhancer region can be active in a cell type specific manner. Optionally, in certain vectors, the promoter and/or enhancer region can be active in all eukaryotic cells, independent of cell type. Preferred promoters of this type are the CMV promoter, the SV40 promoter, the β -actin promoter, the EF1 α promoter, and the retroviral long terminal repeat (LTR).

[141] The vectors also can include, for example, origins of replication and/or markers. A marker gene can confer a selectable phenotype, e.g., antibiotic resistance, on a cell. The marker product is used to determine if the vector has been delivered to the cell and once delivered is being expressed. Examples of selectable markers for mammalian cells are dihydrofolate reductase (DHFR), thymidine kinase, neomycin, neomycin analog G418, hygromycin, puromycin, and blasticidin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective pressure. Examples of other markers include, for example, the *E. coli* lacZ gene, green fluorescent protein (GFP), and luciferase. In addition, an expression vector can include a tag sequence designed to facilitate manipulation or detection (e.g., purification or localization) of the expressed polypeptide. Tag sequences, such as GFP, glutathione S-transferase (GST), polyhistidine, c-myc, hemagglutinin, or FLAGTM tag (Kodak; New Haven, Conn.) sequences typically are expressed as a fusion with the encoded polypeptide. Such tags can be inserted anywhere within the polypeptide including at either the carboxyl or amino terminus.

[142] As used herein, the terms peptide, polypeptide, or protein are used broadly to mean two or more amino acids linked by a peptide bond. Protein, peptide, and polypeptide are also used herein interchangeably to refer to amino acid sequences. It should be recognized that the term polypeptide is not used herein to suggest a particular size or number of amino acids comprising the molecule and that a peptide of the invention can contain up to several amino acid residues or more. As used throughout, subject can be a vertebrate, more specifically a mammal (e.g. a human, horse, cat, dog, cow, pig, sheep, goat, mouse, rabbit, rat, and guinea pig), birds, reptiles, amphibians, fish, and any other animal. The term does not denote a particular age or sex. Thus, adult and newborn subjects, whether male or female, are intended to be covered. As used herein, patient or subject may be used

interchangeably and can refer to a subject with a disease or disorder (e.g. cancer). The term patient or subject includes human and veterinary subjects.

[143] A subject at risk of developing a disease or disorder can be genetically predisposed to the disease or disorder, e.g., have a family history or have a mutation in a gene that causes the disease or disorder, or show early signs or symptoms of the disease or disorder. A subject currently with a disease or disorder has one or more than one symptom of the disease or disorder and may have been diagnosed with the disease or disorder.

[144] The methods and agents as described herein are useful for both prophylactic and therapeutic treatment. For prophylactic use, a therapeutically effective amount of the chimeric polypeptides or chimeric nucleic acid sequences encoding the chimeric polypeptides described herein are administered to a subject prior to onset (e.g., before obvious signs of cancer or inflammation) or during early onset (e.g., upon initial signs and symptoms of cancer or inflammation). Prophylactic administration can occur for several days to years prior to the manifestation of symptoms of cancer or inflammation. Prophylactic administration can be used, for example, in the preventative treatment of subjects diagnosed with a genetic predisposition to cancer. Therapeutic treatment involves administering to a subject a therapeutically effective amount of the chimeric polypeptides or nucleic acid sequences encoding the chimeric polypeptides described herein after diagnosis or development of cancer or inflammation (e.g., an autoimmune disease). Prophylactic use may also apply when a patient is undergoing a treatment, e.g., a chemotherapy, in which inflammation is expected.

[145] According to the methods taught herein, the subject is administered an effective amount of the agent (e.g., a chimeric polypeptide). The terms effective amount and effective dosage are used interchangeably. The term effective amount is defined as any amount necessary to produce a desired physiologic response. Effective amounts and schedules for administering the agent may be determined empirically, and making such determinations is within the skill in the art. The dosage ranges for administration are those large enough to produce the desired effect in which one or more symptoms of the disease or disorder are affected (e.g., reduced or delayed). The dosage should not be so large as to cause substantial adverse side effects, such as unwanted cross-reactions, anaphylactic reactions, and the like. Generally, the dosage will vary with the age, condition, sex, type of disease, the extent of the disease or disorder, route of administration, or whether other drugs are included in the regimen, and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosages can vary and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products.

[146] As used herein the terms treatment, treat, or treating refers to a method of reducing the effects of a disease or condition or symptom of the disease or condition. Thus, in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease or condition or symptom of the disease or condition. For example, a

method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus, the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition.

[147] As used herein, the terms prevent, preventing, and prevention of a disease or disorder refers to an action, for example, administration of the chimeric polypeptide or nucleic acid sequence encoding the chimeric polypeptide, that occurs before or at about the same time a subject begins to show one or more symptoms of the disease or disorder, which inhibits or delays onset or exacerbation of one or more symptoms of the disease or disorder. As used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level. Such terms can include but do not necessarily include complete elimination.

[148] Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

[149] Publications cited herein and the material for which they are cited are hereby specifically incorporated by reference in their entireties.

EXAMPLES

[150] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided herein.

Example 1: Protease cleavage of fusion protein by MMP9 protease

[151] One of skill in the art would be familiar with methods of setting up protein cleavage assay. 100ug of protein in 1xPBS pH 7.4 were cleaved with 1 ug active MMP9 (Sigma catalog # SAE0078-50 or Enzo catalog BML-SE360) and incubated at room temperature for up to 16 hours. Digested protein can be subsequently used in functional assays or stored at -80°C prior to testing. Extent of cleavage was monitored by SDS PAGE using methods well known in the art. As shown in FIG. 9.

Example 2: HEK Blue assay

[152] HEK-Blue IL12 cells (InvivoGen) were plated in suspension at a concentration of 250,000 cells/well in culture media with or without 40mg/ml human serum albumin (HSA) and stimulated with a dilution series of recombinant hIL12, chimeric IL12 (mouse p35/human p40) or activatable hIL12 for 24 hours at 37°C and 5% CO₂. Activity of uncleaved and cleaved activatable hIL12 was tested. Cleaved inducible hIL12 was generated by incubation with active MMP9. IL12 activity was assessed by quantification of Secreted Alkaline Phosphatase (SEAP) activity using the reagent QUANTI-Blue (InvivoGen), a colorimetric based assay. As shown in FIGs. 7, 8, 11, and 13.

Example 3: Splenocyte T-Blast assay

[153] T-Blasts were induced from murine splenocytes with a 6-day incubation with PHA and a 24hr incubation with recombinant hIL12. Tblasts were then plated in suspension at a concentration of 200,000 cells/well in culture media with or without 40mg/ml human serum albumin (HSA) and stimulated with a dilution series of recombinant hIL12 or chimeric IL12 (mouse p35/human p40) or mouse IL12 for 72 hours at 37°C and 5% CO₂. Activity of uncleaved and cleaved IL12 was tested. Cleaved inducible hIL12 was generated by incubation with active MMP9. IL12 activity was assessed by downstream quantification of IFN γ production using a mIFN γ alphaLISA.

Example 4: *In Vivo* Delivery of a Protease Activated Fusion Protein Results in Decreased Tumor Growth

[154] The chimeric polypeptide is examined to determine if it could have biological effects *in vivo*. For these experiments a system is used in which tumor cells injected intraperitoneally rapidly and preferentially attach and grow initially on the milky spots, a series of organized immune aggregates found on the omentum (Gerber et al., Am. J. Pathol. 169:1739-52 (2006)). This system offers a convenient way to examine the effects of fusion protein treatment on tumor growth since fusion proteins can be delivered intraperitoneally multiple times and tumor growth can be analyzed by examining the dissociated omental cells. For these experiments, the Colon 38 cell line, a rapidly growing tumor cell line that expresses both MMP2 and MMP9 *in vitro*, may be used. The omental tissue normally expresses a relatively small amount of MMP2 and MMP9, but, when Colon 38 tumor is present on the omentum, MMP levels increase. Using this tumor model, the ability of IL-2 mutein

fusion proteins to affect tumor growth is examined. Colon 38 cells are injected intraperitoneally, allowed to attach and grow for 1 day, and then treated daily with fusion protein interaperitoneally. At day 7, the animals are sacrificed and the omenta examined for tumor growth using flow cytometry and by a colony-forming assay.

Example 5: Construction of an Exemplary Activatable Interleukin Protein Targeting CD20

Generation of an activatable interleukin domain

[155] The human IL-12p35 chain canonical sequence is Uniprot Accession No. P29459. The human IL-12p40 chain canonical sequence is Uniprot Accession No. P29460. IL-12p35 and IL-12p40 are cloned into an expression construct. A protease cleavage site is included between the IL-12p35 and IL-12p40 domains. An IL-12 polypeptide capable of binding to CD20 polypeptide present in a tumor or on a tumor cell is produced as follows. A nucleic acid is produced that contains nucleic acid sequences: (1) encoding an IFN γ polypeptide sequence and (2) one or more polypeptide linkers. Activatable interleukin plasmid constructs can have optional Flag, His or other affinity tags, and are electroporated into HEK293 or other suitable human or mammalian cell lines and purified. Validation assays include T cell activation assays using T cells responsive to IL-12 stimulation in the presence of a protease.

Generation of a scFv CD20 binding domain

[156] CD20 is one of the cell surface proteins present on B-lymphocytes. CD20 antigen is found in normal and malignant pre-B and mature B lymphocytes, including those in over 90% of B-cell non-Hodgkin's lymphomas (NHL). The antigen is absent in hematopoietic stem cells, activated B lymphocytes (plasma cells) and normal tissue. As such, several antibodies mostly of murine origin have been described: 1F5, 2B8/C2B8, 2H7, and 1H4.

[157] Human or humanized anti-CD20 antibodies are therefore used to generate scFv sequences for CD20 binding domains of an activatable interleukin protein. DNA sequences coding for human or humanized VL and VH domains are obtained, and the codons for the constructs are, optionally, optimized for expression in cells from Homo sapiens. The order in which the VL and VH domains appear in the scFv is varied (i.e., VL-VH, or VH-VL orientation), and three copies of the "G4S" (SEQ ID NO: 87) or "G₄S" (SEQ ID NO: 87) subunit (G₄S)₃ (SEQ ID NO: 90) connect the variable domains to create the scFv domain. Anti-CD20 scFv plasmid constructs can have optional Flag, His or other affinity tags, and are electroporated into HEK293 or other suitable human or mammalian cell lines and purified. Validation assays include binding analysis by FACS, kinetic analysis using Proteon, and staining of CD20-expressing cells.

Cloning of DNA expression constructs encoding the activatable interleukin protein

REPLACEMENT SHEET

Attorney Docket No. 761146.000022

[158] The activatable interleukin construct with protease cleavage site domains are used to construct an activatable interleukin protein in combination with an anti-CD20 scFv domain and a serum half-life extension element (e.g., a HSA binding peptide or VH domain), as shown in Fig. 10. For expression of an activatable interleukin protein in CHO cells, coding sequences of all protein domains are cloned into a mammalian expression vector system. In brief, gene sequences encoding the activatable interleukin domain, serum half-life extension element, and CD20 binding domain along with peptide linkers L1 and L2 are separately synthesized and subcloned. The resulting constructs are then ligated together in the order of CD20 binding domain ~ L1 ~ IL-12p35 ~ L2 ~ protease cleavage domain ~ L3 ~ IL-12p40 ~ L4 ~ anti-CD20 scFv ~ L5 ~ serum half-life extension element to yield a final construct. All expression constructs are designed to contain coding sequences for an N-terminal signal peptide and a C-terminal hexahistidine (6xHis)-tag (SEQ ID NO: 91) to facilitate protein secretion and purification, respectively.

Expression of activatable interleukin proteins in stably transfected CHO cells

[159] A CHO cell expression system (Flp-In®, Life Technologies), a derivative of CHO-K1 Chinese Hamster ovary cells (ATCC, CCL-61) (Kao and Puck, Proc. Natl. Acad. Sci. USA 1968;60(4):1275-81), is used. Adherent cells are subcultured according to standard cell culture protocols provided by Life Technologies.

[160] For adaption to growth in suspension, cells are detached from tissue culture flasks and placed in serum-free medium. Suspension-adapted cells are cryopreserved in medium with 10% DMSO.

[161] Recombinant CHO cell lines stably expressing secreted activatable interleukin proteins are generated by transfection of suspension-adapted cells. During selection with the antibiotic Hygromycin B viable cell densities are measured twice a week, and cells are centrifuged and resuspended in fresh selection medium at a maximal density of 0.1×10^6 viable cells/mL. Cell pools stably expressing activatable interleukin proteins are recovered after 2-3 weeks of selection at which point cells are transferred to standard culture medium in shake flasks. Expression of recombinant secreted proteins is confirmed by performing protein gel electrophoresis or flow cytometry. Stable cell pools are cryopreserved in DMSO containing medium.

[162] Activatable interleukin proteins are produced in 10-day fed-batch cultures of stably transfected CHO cell lines by secretion into the cell culture supernatant. Cell culture supernatants are harvested after 10 days at culture viabilities of typically >75%. Samples are collected from the production cultures every other day and cell density and viability are assessed. On day of harvest, cell culture supernatants are cleared by centrifugation and vacuum filtration before further use.

[163] Protein expression titers and product integrity in cell culture supernatants are analyzed by SDS-PAGE.

Purification of activatable interleukin proteins

[164] Activatable interleukin proteins are purified from CHO cell culture supernatants in a two-step procedure. The constructs are subjected to affinity chromatography in a first step followed by preparative size exclusion chromatography (SEC) on Superdex 200 in a second step. Samples are buffer-exchanged and concentrated by ultrafiltration to a typical concentration of >1 mg/mL. Purity and homogeneity (typically >90%) of final samples are assessed by SDS PAGE under reducing and non-reducing conditions, followed by immunoblotting using an anti-HSA or anti idiotypic antibody as well as by analytical SEC, respectively. Purified proteins are stored at aliquots at -80°C until use.

Example 6: Determination of antigen affinity by flow cytometry

[165] The activatable interleukin proteins of the preceding examples are tested for their binding affinities to human CD20⁺ cells and cynomolgus CD20⁺ cells.

[166] CD20⁺ cells are incubated with 100 μ L of serial dilutions of the activatable interleukin proteins of the preceding examples and at least one protease. After washing three times with FACS buffer the cells are incubated with 0.1 mL of 10 μ g/mL mouse monoclonal anti-idiotypic antibody in the same buffer for 45 min on ice. After a second washing cycle, the cells are incubated with 0.1 mL of 15 μ g/mL FITC-conjugated goat anti-mouse IgG antibodies under the same conditions as before. As a control, cells are incubated with the anti-His IgG followed by the FITC-conjugated goat anti-mouse IgG antibodies without the activatable interleukin proteins. The cells were then washed again and resuspended in 0.2 mL of FACS buffer containing 2 μ g/mL propidium iodide (PI) in order to exclude dead cells. The fluorescence of 1×10^4 living cells is measured using a Beckman-Coulter FC500 MPL flow cytometer using the MXP software (Beckman-Coulter, Krefeld, Germany) or a Millipore Guava EasyCyte flow cytometer using the Incyte software (Merck Millipore, Schwalbach, Germany). Mean fluorescence intensities of the cell samples are calculated using CXP software (Beckman-Coulter, Krefeld, Germany) or Incyte software (Merck Millipore, Schwalbach, Germany). After subtracting the fluorescence intensity values of the cells stained with the secondary and tertiary reagents alone the values are then used for calculation of the K_D values with the equation for one-site binding (hyperbola) of the GraphPad Prism (version 6.00 for Windows, GraphPad Software, La Jolla California USA).

[167] CD20 binding and crossreactivity are assessed on the human CD20⁺ tumor cell lines. The K_D ratio of crossreactivity is calculated using the K_D values determined on the CHO cell lines expressing either recombinant human or recombinant cynomolgus antigens.

Example 7: Cytotoxicity Assay

[168] The activatable interleukin protein of the preceding examples is evaluated *in vitro* on its mediation of immune response to CD20⁺ target cells.

[169] Fluorescence labeled CD20⁺ REC-1 cells (a Mantle cell lymphoma cell line, ATCC CRL-3004) are incubated with isolated PBMC of random donors or CB15 T-cells (standardized T-cell line)

as effector cells in the presence of the activatable interleukin protein of the preceding examples and at least one protease. After incubation for 4 h at 37°C in a humidified incubator, the release of the fluorescent dye from the target cells into the supernatant is determined in a spectrofluorimeter. Target cells incubated without the activatable interleukin protein of the preceding examples and target cells totally lysed by the addition of saponin at the end of the incubation serve as negative and positive controls, respectively.

[170] Based on the measured remaining living target cells, the percentage of specific cell lysis is calculated according to the following formula: $[1 - (\text{number of living targets}_{\text{sample}} / \text{number of living targets}_{\text{spontaneous}})] \times 100\%$. Sigmoidal dose response curves and EC_{50} values are calculated by non-linear regression/4-parameter logistic fit using the GraphPad Software. The lysis values obtained for a given antibody concentration are used to calculate sigmoidal dose-response curves by 4 parameter logistic fit analysis using the Prism software.

Example 8: Pharmacokinetics of activatable interleukin proteins

[171] The activatable interleukin protein of the preceding examples is evaluated for half-time elimination in animal studies.

[172] The activatable interleukin protein is administered to cynomolgus monkeys as a 0.5 mg/kg bolus injection into the saphenous vein. Another cynomolgus monkey group receives a comparable cytokine in size, but lacking a serum half-life extension element. A third and fourth group receive a cytokine with serum half-life extension elements and a cytokine with CD20 and serum half-life extension elements respectively, and both comparable in size to the activatable interleukin protein. Each test group consists of 5 monkeys. Serum samples are taken at indicated time points, serially diluted, and the concentration of the proteins is determined using a binding ELISA to CD20.

[173] Pharmacokinetic analysis is performed using the test article plasma concentrations. Group mean plasma data for each test article conforms to a multi-exponential profile when plotted against the time post-dosing. The data are fit by a standard two-compartment model with bolus input and first-order rate constants for distribution and elimination phases. The general equation for the best fit of the data for i.v. administration is: $c(t) = Ae^{-\alpha t} + Be^{-\beta t}$, where $c(t)$ is the plasma concentration at time t , A and B are intercepts on the Y-axis, and α and β are the apparent first-order rate constants for the distribution and elimination phases, respectively. The α -phase is the initial phase of the clearance and reflects distribution of the protein into all extracellular fluid of the animal, whereas the second or β -phase portion of the decay curve represents true plasma clearance. Methods for fitting such equations are well known in the art. For example, $A = D/V(\alpha - k_{21})/(\alpha - \beta)$, $B = D/V(\beta - k_{21})/(\alpha - \beta)$, and α and β (for $\alpha > \beta$) are roots of the quadratic equation: $r^2 + (k_{12} + k_{21} + k_{10})r + k_{21}k_{10} = 0$ using estimated parameters of V =volume of distribution, k_{10} =elimination rate, k_{12} =transfer rate from compartment 1 to compartment 2 and k_{21} =transfer rate from compartment 2 to compartment 1, and D =the administered dose.

[174] Data analysis: Graphs of concentration versus time profiles are made using KaleidaGraph (KaleidaGraph™ V. 3.09 Copyright 1986-1997. Synergy Software. Reading, Pa.). Values reported as less than reportable (LTR) are not included in the PK analysis and are not represented graphically. Pharmacokinetic parameters are determined by compartmental analysis using WinNonlin software (WinNonlin® Professional V. 3.1 WinNonlin™ Copyright 1998-1999. Pharsight Corporation. Mountain View, Calif.). Pharmacokinetic parameters are computed as described in Ritschel W A and Kearns G L, 1999, IN: *Handbook Of Basic Pharmacokinetics Including Clinical Applications*, 5th edition, American Pharmaceutical Assoc., Washington, D.C.

[175] It is expected that the activatable interleukin protein of the preceding examples has improved pharmacokinetic parameters such as an increase in elimination half-time as compared to proteins lacking a serum half-life extension element.

Example 9: Xenograft Tumor Model

[176] The activatable interleukin protein of the preceding examples is evaluated in a xenograft model.

[177] Female immune-deficient NOD/scid mice are sub-lethally irradiated (2 Gy) and subcutaneously inoculated with 4×10^6 Ramos RA1 cells into the right dorsal flank. When tumors reach 100 to 200 mm³, animals are allocated into 3 treatment groups. Groups 2 and 3 (8 animals each) are intraperitoneally injected with 1.5×10^7 activated human T-cells. Three days later, animals from Group 3 are subsequently treated with a total of 9 intravenous doses of 50 µg activatable interleukin protein of the preceding examples (qdx9d). Groups 1 and 2 are only treated with vehicle. Body weight and tumor volume are determined for 30 days.

[178] It is expected that animals treated with the activatable interleukin protein of the preceding examples have a statistically significant delay in tumor growth in comparison to the respective vehicle-treated control group.

[179] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Example 10: MC38 experiments

The MC38 cell line, a rapidly growing colon adenocarcinoma cell line that expresses MMP9 *in vitro*, was used. Using this tumor model, the ability of fusion proteins to affect tumor growth was examined.

Example 10a: MC38 IFNα and IL-12

Agents and Treatment:

Gr.	N	Agent	Formulation dose	Route	Schedule
1 [#]	12	Vehicle	-	ip	biwk x 3
2	8	ACP11	17.5 µg/animal	ip	biwk x 3
3	8	ACP11	175 µg/animal	ip	biwk x 3
4	8	ACP11	525 µg/animal	ip	biwk x 3
13	8	IL-12-HM-WTI	2 µg/animal	ip	bid x 5 then 2-day pause then bid x 5 then 2-day pause
14	8	IL-12-HM-WTI	10 µg/animal	ip	bid x 5 then 2-day pause then bid x 5 then 2-day pause

#- Control Group

Procedures:

Mice were anaesthetized with isoflurane for implant of cells to reduce the ulcerations. CR female C57BL/6 mice were set up with 5×10^5 MC38 tumor cells in 0% Matrigel sc in flank. Cell Injection Volume was 0.1 mL/mouse. Mouse age at start date was 8 to 12 weeks. Pair matches were performed when tumors reach an average size of 100 - 150 mm³ and begin treatment. Body weights were taken at initiation and then biweekly to the end. Caliper measurements were taken biweekly to the end. Any adverse reactions were to be reported immediately. Any individual animal with a single observation of > than 30% body weight loss or three consecutive measurements of >25% body weight loss was euthanized. Any group with a mean body weight loss of >20 % or >10% mortality stopped dosing; the group was not euthanized and recovery is allowed. Within a group with >20% weight loss, individuals hitting the individual body weight loss endpoint were euthanized. If the group treatment related body weight loss is recovered to within 10% of the original weights, dosing resumed at a lower dose or less frequent dosing schedule. Exceptions to non-treatment body weight % recovery were allowed on a case-by-case basis. Endpoint was tumor growth delay (TGD). Animals were monitored individually. The endpoint of the experiment was a tumor volume of 1500 mm³ or 45 days, whichever comes first. Responders were followed longer. When the endpoint was reached, the animals are to be euthanized.

Example 11: Conditionally Active Fusion Proteins That Contain a Blocking Moiety that is a Serum Albumin Binding Domain

[180] This example describes the production and activity of fusion proteins, preferably cytokines,

that have inducible activity, i.e., they are inactive until induced, typically by separation of a blocking moiety from the active moiety upon cleavage of a linker between the blocking moiety and the active moiety. The fusion proteins contain a single antibody variable domain (a dAb) that binds serum albumin via the CDR loops, and binds to an active moiety (here an anti-CD3 scFV) via one or more non-CDR loops (e.g., the C loop). The serum albumin-binding blocking moiety is operably linked to the active moiety through a protease cleavable linker, and active moiety is operably linked to a targeting domain (here an anti-epidermal growth factor receptor (EGFR) dAb or anti-prostate-specific membrane antigen (PSMA) dAb) through a linker that is not protease cleavable. These fusion proteins can be administered as inactive proteins that become activated upon cleavage of the protease cleavable linker and subsequent release of the inhibitory albumin-binding domain. The anti-CD3 scFV in the fusion proteins is a surrogate for a desired cytokine in the fusion proteins described in this disclosure. Similar fusion proteins that contain a desired cytokine (e.g., IL-2, IL-12, an Interferon) or functional fragment or mutein thereof, a targeting domain and an albumin-binding dAb that also binds and inhibits the cytokine or functional fragment or mutein thereof can be prepared using the methods described and exemplified herein. Anti-serum albumin dAb that bind and inhibit the activity of a desired cytokine or functional fragment or mutein thereof can provide both steric masking of the cytokine (through the cytokines proximity to bound serum albumin) and specific masking of the cytokine (through binding to cytokine via the non-CDR loop (e.g., the C loop)). Anti-serum albumin dAb that bind and inhibit the activity of a desired cytokine or functional fragment or mutein thereof can be obtained using suitable methods, such as by introducing amino acid sequence diversity into the non-CDR loops (e.g., C loop) of an anti-serum albumin binding dAb and screening for binding to the desired cytokine. Any suitable methods can be used for the selection, such as phage display. For example, an exemplary anti-serum albumin dab that can be used has the following sequence, and the amino acid sequence in the C loop (Bold Underlined) can be diversified (e.g., randomized) and resulting dAbs screened for binding to serum albumin via CDR interaction and to cytokine via non-CDR loop interaction. If desired, the amino acid sequence of a known cytokine binding peptide can be grafted into the C loop.

EVQLVESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQ**GGGGGLDGNEEPGG**LEWVSSI
SGSGRDTLYADSVKGRFTISRDNKTTLYLQMNSLRPEDTAVYYCTIGGSLVSSQGTLVTVS
S (SEQ ID NO: 92)

A. Protease activation of ProTriTAC leads to significantly enhanced activity *in vitro*

[181] Purified ProTriTAC (prodrug), non-cleavable ProTriTAC [prodrug (non-cleavable)], and recombinant active drug fragment mimicking the protease-activated ProTriTAC (active drug) were tested for binding to recombinant human CD3 in an ELISA assay, binding to purified human primary T cells in a flow cytometry assay, and functional potency in a T cell-dependent cellular cytotoxicity

assay.

[182] For ELISA, soluble ProTriTAC proteins at the indicated concentrations were incubated with immobilized recombinant human CD3e (R&D Systems) for 1 h at room temperature in PBS supplemented with 15 mg/ml human serum albumin. Plates were blocked using SuperBlock (Thermo Fisher), washed using PBS with 0.05% Tween-20, and detected using a non-competitive anti-CD3 idiotype monoclonal antibody 11D3 followed by peroxidase-labeled secondary antibody and TMB-ELISA substrate solution (Thermo Fisher).

[183] For flow cytometry, soluble ProTriTAC proteins at the indicated concentrations were incubated with purified human primary T cells for 1 h at 4°C in the presence of PBS with 2% fetal bovine serum and 15 mg/ml human serum albumin. Plates were washed with PBS with 2% fetal bovine serum, detected using AlexaFluor 647-labeled non-competitive anti-CD3 idiotype monoclonal antibody 11D3, and data was analyzed using FlowJo 10 (FlowJo, LLC).

[184] For functional potency in a T cell-dependent cellular cytotoxicity assays, soluble ProTriTAC proteins at the indicated concentrations were incubated with purified resting human T cells (effector cell) and HCT116 cancer cell (target cell) at 10:1 effector:target cell ratio for 48 h at 37°C. The HCT116 target cell line has been stably transfected with a luciferase reporter gene to allow specific T cell-mediated cell killing measurement by ONE-Glo (Promega).

B. ProTriTAC exhibits potent, protease-dependent, anti-tumor activity in a rodent tumor xenograft model

[185] ProTriTAC was evaluated for their anti-tumor activity in vivo in an HCT116 subcutaneous xenograft tumor admixed with expanded human T cells in immunocompromised NCG mice. Specifically, 5x10⁶ HCT116 cells were admixed with 2.5x10⁶ expanded T cells per mouse on day 0. Dosing of ProTriTACs were performed starting on the following day with a q.d. x 10 schedule via intraperitoneal injection. Tumor volume measurements were determined using caliper measurements and calculated using the formula $V = (\text{length} \times \text{width} \times \text{width}) / 2$ at the indicated times.

C. Expression, purification and stability of exemplary ProTriTAC trispecific molecules Protein Production

[186] Sequences encoding inducible fusion protein molecules were cloned into mammalian expression vector pcDNA 3.4 (Invitrogen) preceded by a leader sequence and followed by a 6x Histidine Tag (SEQ ID NO: 91). Expi293F cells (Life Technologies A14527) were maintained in suspension in Optimum Growth Flasks (Thomson) between 0.2 to 8 x 10⁶ cells/ml in Expi 293 media. Purified plasmid DNA was transfected into Expi293 cells in accordance with Expi293 Expression System Kit (Life Technologies, A14635) protocols, and maintained for 4-6 days post transfection. Alternatively sequences encoding the fusion protein molecules were cloned into mammalian expression vector pDEF38 (CMC ICOS) transfected into CHO-DG44 dhfr- cells, stable pools

generated, and cultured in production media for up to 12 days prior to purification. The amount of the exemplary fusion proteins in conditioned media was quantified using an Octet RED 96 instrument with Protein A tips (ForteBio / Pall) using a control fusion protein for a standard curve. Conditioned media from either host cell was filtered and partially purified by affinity and desalting chromatography. Fusion proteins were subsequently polished by ion exchange and upon fraction pooling formulated in a neutral buffer containing excipients. Final purity was assessed by SDS-PAGE and analytical SEC using an Acquity BEH SEC 200 1.7u 4.6 x 150mm column (Waters Corporation) resolved in an aqueous/organic mobile phase with excipients at neutral pH on a 1290 LC system and peaks integrated with Chemstation CDS software (Agilent). Fusion proteins purified from CHO host cells are shown in the SDS-PAGE depicted below.

Stability Assessment

[187] Purified fusion proteins in two formulations were sub-aliquoted into sterile tubes and stressed by five freeze-thaw cycles each comprising greater than 1 hour at -80°C and room temperature or by incubation at 37°C for 1 week. Stressed samples were evaluated for concentration and turbidity by UV spectrometry using UV transparent 96 well plates (Corning 3635) with a SpectraMax M2 and SoftMaxPro Software (Molecular Devices), SDS-PAGE, and analytical SEC and compared to the same analysis of control non-stressed samples. An overlay of chromatograms from analytical SEC of control and stressed samples for a single exemplary ProTriTAC molecule purified from 293 host cells is depicted below.

[188] The results show that ProTriTACs were produced in comparable yields to regular TriTACs from CHO stable pools; and that the proteins were stable after repeated freeze-thaws and 37°C for 1 week.

D. Demonstration of functional masking and stability of ProTriTAC in vivo in a three-week cynomolgus monkey pharmacokinetic study

[189] Single dose of PSMA-targeting ProTriTAC (SEQ ID NO: 74), non-cleavable ProTriTAC (SEQ ID NO: 75), non-masked/non-cleavable TriTAC (SEQ ID NO: 78), and active drug mimicking protease-activated ProTriTAC (SEQ ID NO: 76) was dosed into cynomolgus monkeys at 0.1 mg/kg via intravenous injection. Plasma samples were collected at the indicated time points. ProTriTAC concentrations were determined using ligand binding assays with biotinylated recombinant human PSMA (R&D systems) and sulfo-tagged anti-CD3 idiotype antibody cloned 11D3 in a MSD assay (Meso Scale Diagnostic, LLC). Pharmacokinetic parameters were estimated using Phoenix WinNonlin pharmacokinetic software using a non-compartmental approach consistent with the intravenous bolus route of administration.

[190] To calculate the rate of in vivo prodrug conversion, the concentration of active drug in circulation was estimated by solving the following system of differential equations where P is the concentration of prodrug, A is the concentration of active drug, k_a is the rate of prodrug activation in

circulation, $k_{c,P}$ is the clearance rate of the prodrug, and $k_{c,A}$ is the clearance rate of the active drug.

$$\frac{dP}{dt} = -k_{c,P}P$$

$$\frac{dA}{dt} = k_aP - k_{c,A}A$$

[191] The clearance rates of the prodrug, active drug, and a non-cleavable prodrug control ($k_{c,NCLV}$) were determined empirically in cynomolgus monkeys. To estimate the rate of prodrug activation in circulation, we assumed that the difference between the clearance rate of cleavable prodrug and non-cleavable prodrug arose solely from non-specific activation in circulation. Therefore, the rate of prodrug conversion to active drug in circulation was estimated by subtracting the clearance rate of the cleavable prodrug from the non-cleavable prodrug.

$$k_a = k_{c,NCLV} - k_{c,P}$$

[192] The initial concentration of prodrug in circulation was determined empirically and the initial concentration of active drug was assumed to be zero.

Results and Discussion

[193] The results of this Example 11 show that fusion proteins that contain a polypeptide with desired therapeutic activity, such as a cytokine or functional fragment or mutein thereof or anti-CD3 scFV, can be prepared in which the therapeutic activity is masked by a masking domain that binds to both serum albumin and to the active polypeptide. The masking domain is operably linked to the active domain through a protease cleavable linker. The results show that this type of fusion protein can be administered as an inactive protein that becomes activated upon protease cleavage at the desired location of therapeutic activity, such as, at a tumor.

[194] Amino acid sequences of fusion proteins used in Example 11 are given as SEQ ID NOs: 71-78.

[195] Sample fusion protein constructs are detailed in Table 3. In table 3, “L” is an abbreviation of “linker”, and “cleav. link.” is an abbreviation of “cleavable linker”. Other abbreviations “mIFNg” indicates mouse interferon gamma (IFNg); “hAlbumin” indicates human serum albumin (HSA); “mAlbumin” indicates mouse serum albumin.

Table 3: CONSTRUCT PERMUTATION TABLE

Construct Name	Construct Description
ACP63	anti-FN CGS-2 scFv (Vh/VI)-6xHis
ACP04	human p40-murine p35-6xHis
ACP05	human p40-human p35-6xHis
ACP34	mouse p35-(cleav. link.)-mouse p40-6xHis
ACP35	mouse p35-GS-(cleav. link.)-GS-mouse p40-6xHis
ACP36	(anti-HSA)-(cleav. link.)-mouse p40-mouse p35-(cleav. link.)-(anti-HSA)-6xHis
ACP37	(anti-EpCAM)-(anti-HSA)-(cleav. link.)-mouse p40-mouse p35-(cleav. link.)-(anti-HSA)-6xHis
ACP79	(anti-EpCAM)-Linker-(anti-HSA)-(cleav. link.r)-mIL12-(cleav. link.)-(Anti-HSA)-6xHis
ACP80	(anti-HSA)-(cleav. link.)-mIL12-(cleav. link.)-(anti-HSA)-Linker-(anti-EpCAM)-6xHis
ACP06	Blocker12-Linker-(cleav. link.)-human p40-Linker-mouse p35-(cleav. link.)-(anti-HSA)-6xHis
ACP07	Blocker12-Linker-(cleav. link.)-human p40-Linker-mouse p35-(cleav. link.)-(anti-HSA)-Linker-(anti-FOLR1)-6xHis
ACP08	(anti-FOLR1)-Linker-Blocker12-Linker-(cleav. link.)-human p40-Linker-mouse p35-(cleav. link.)-(anti-HSA)-6xHis
ACP09	(anti-HSA)-Linker-Blocker12-Linker-(cleav. link.)-human p40-Linker-mouse p35-6xHis
ACP10	(anti-HSA)-(cleav. link.)-human p40-L-mouse p35-(cleav. link.)-Linker-Blocker12-6xHis
ACP11	hp40-Linker-mp35-(cleav. link.)-Linker-Blocker12-Linker-(anti-HSA)-6xHis
ACP91	human_p40-Linker-mouse_p35-Linker-Linker-Blocker-Linker-(anti-HSA)_(non-cleavable control)
ACP136	human p40-L-mouse p35-XL-Blocker
ACP138	human_p40-L-mouse_p35-XL-Blocker-L-HSA-L-FOLR1
ACP139	FOLR1-L-human_p40-L-mouse_p35-XL-Blocker-L-HSA
ACP140	FOLR1-(cleav. link.)-human_p40-L-mouse_p35-XL-Blocker-L-HSA
ACP117	anti-FN CGS-2 scFv (Vh/VI)-6xHis

Sequence Table

SEQ ID NO.	Name	Sequence

1	Human serum albumin	MKWVTFISLL FLFSSAYSRG VFRRDAHKSE VAHRFKDLGE ENFKALVLIA FAQYLQQCPF EDHVKL VNEV TEFATCTVAD ESAENCCKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPPLRLV RPEVDVMCTA FHDNEETFLK KYLYEIARRH PYFYAPELLF FAKRYKAAFT ECCQAADKAA CLLPKLDEL R DEGKASSAKQ GLKCASLQKF GERAFAKAWAV ARLSQRFPKA EFAEVSKLVT DLT KVHTECC HGD LLECADD RADLAKYICE NQDSISSKLK ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVGSKDVC KNYAEAKDVF LGMFLYEYAR RHPDYSV VLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN LIKQNCSELF QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV SRNLGKVGSK CCKHPEAKRM PCAEDCLSVF LNQLCVLHEK TPVSDRVTKC CTESLVNGRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALV ELVKHK PKATKEQLKAVMDDFAAFVEKCKKADDKET CFAEEGKKLVAASQAALGL
44	ACP04 (human p40/murine p35 IL12 fusion protein)	iwelkkdvyyvvel dwypdaggemvvl tcdtpeedgitwldqssevlsgsktltiqvkefgdagqytchkggevlshsl lllhkk edgiwstdilkdqkepkntflrceaknysgrftcwwltistdltsvkssrgssdpqgvtcgaatlsaervrgdnkeyeysvecq edsacpaaeeslpievmdavhklkyenytsffirdiikpdpknqlkplknsrqvevswyepdtwstphsyfsltfcvqvqg kskrekkdrvftdkt satvicrk nasisvraqdryssswsewasvpcsgggsgggsgggsgggsvipvs gparclsqsrnlkkt ddmvktareklkhsctaedidheditr dqtstlktclplelhknesclatretsstrgslppqktslmmtlclgsiyedlkmyqte fqainaalqnhnhqqiildkgmlvaidelmqslnhngetlrqkppvg eadpyrvkmklcillhafstrvvtinrmgy lssaHH HHHH
45	ACP05 (human p40/murine p35 IL12 fusion protein)	iwelkkdvyyvvel dwypdaggemvvl tcdtpeedgitwldqssevlsgsktltiqvkefgdagqytchkggevlshsl lllhkk edgiwstdilkdqkepkntflrceaknysgrftcwwltistdltsvkssrgssdpqgvtcgaatlsaervrgdnkeyeysvecq edsacpaaeeslpievmdavhklkyenytsffirdiikpdpknqlkplknsrqvevswyepdtwstphsyfsltfcvqvqg kskrekkdrvftdkt satvicrk nasisvraqdryssswsewasvpcsgggsgggsgggsgggsvrnl pvatpdp gmfpc lhh qnllravsnmlqkarqtlefypctseeidheditkdktstveaclpleltknesclnsretsf itngsclsrktsfmmalclssiye dlk myqveftmnakllmdpkrqifldqnm lavidelmqalnfns etvpqkssleepdfytkiklcillhafiravtidrvmsylna sHHHHHH
46	ACP06 (human p40/murine p35 IL12 fusion protein)	QSVLTQPPSVSGAPGQRTV TISCSGSR SNIGSNTVKWYQQLPGTAPKLLIYYNDQRPSG VPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDRYTHPALLFGTGTKVTVLggggs gggsggggsQVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AFIRYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCKTHGSHDN WGQGTMTVTVSSgggsgggsgggsgggsgggsgggsgggsgggSGGPGPAGMKGLPGSiwelkkdvyyv eldwypdaggemvvl tcdtpeedgitwldqssevlsgsktltiqvkefgdagqytchkggevlshsl lllhkkedgiwstdilkd qkepkntflrceaknysgrftcwwltistdltsvkssrgssdpqgvtcgaatlsaervrgdnkeyeysvecqedsacpaaeesl pievmdavhklkyenytsffirdiikpdpknqlkplknsrqvevswyepdtwstphsyfsltfcvqvqgkskrekkdrvft dkt satvicrk nasisvraqdryssswsewasvpcsgggsgggsgggsgggsvipvs gparclsqsrnlkktddmvktarekl

[illegible]

[illegible]

[illegible]

54	IL12Rb-	10 20 30 40 50
	2	WAKLPGGSL AEMKILINLL IERKIDEEKA GGVVKEEEMV ILLGSEINXLI 60 70 80 90 100 GSLKPGGCKA WISERKULLL VKEDARINER HGRILNSQVI GLRLGILLEV 110 120 130 140 150 GKLACINSEK IYICGAEIEV GWAPKQFQNL SCIQKGGQGI VACTIKERGRD 160 170 180 190 200 THLYTETILQ LAGPENLITQ KCKKDIKCYK LEEVAILERK ARESNFIKAV 210 220 230 240 250 TAVNSLGERS SLPSITITELQ IYRELEPKEL PIKTCOKAVS SCILYKEDGG 260 270 280 290 300 LVLLHRLVYR EENKELNNKV NUIKAKGSHD LLELKEKIKI EKQIESKIML 310 320 330 340 350 YKGSSEKMER SLRAQIFEEK PTGNLEVKYM KKHILVSSQI IALEKKNLSV 360 370 380 390 400 SESSGKILKY QYLLQALLTG KANIKNIIIGH IAKTIVIRGI GNVAVVYAA 410 420 430 440 450 WKKGSLETER INIMNLCENK LIAPKQVSNM SAGKNNIAYI KQPEEKEEBA 460 470 480 490 500 VQEVVYKKE LHEGSEIKVE LNELASPKYM VSAIIEEIKI EXICIRIKVI 510 520 530 540 550 ALSGRGGCKA SILGNKMKKA PLGGKINIAI TPKGSIKIS ENAIEVQKYM 560 570 580 590 600 GELLHYEIKM KERRAKSGRW LCEIKIPVSG NARFINAKGP EVYVILKNTA 610 620 630 640 650 IALGSESHG NEKEPCLOEK ANKNATVAPK ICIALIKVGI ESHVVEKGV 660 670 680 690 700 KLLALARRK KESSEIKDRA NAKKAKIEL KKKIKLELD ALLIKSEKE 710 720 730 740 750 KREELVISEV LKQYIEVTER EPCNKVQRE KGIQKHQAGE KRRKHGASSR 760 770 780 790 800 KREKALAKES SOLVETAKVL ESRKADKKEE NEACKEVILA AGELATKGG 810 820 830 840 850 LPSNIDLES NEAPLADSL ELESCHISLS VERESALHPL TEGGEGKIL 860 DLEKMRGCSL ML
55	IL12Rb-	10 20 30 40 50
	1	MEPLVTFVVF LLEFLFLSRQ GAACRISQCC FQDPYPFDAD SGASAGPRDL 60 70 80 90 100 RCYRISSDAY EGSWQYESPT AGVSHFLACC LSSGRCCYFA AGSATRIQFS 110 120 130 140 150 EQAGVSVLYT VTLWVESWAR NQTERKPEVT LQLYNEVKYE PPLGDIKVK 160 170 180 190 200 LAGQLRWWE IPDNQVCAEV QFRHRTPEEP WKLGDGCPQD DETESCLCP 210 220 230 240 250 EMVVAQEFQL PRRQLSGQGS SWSKNSSPVC VPENPFPQV VRFSVEQLGQ 260 270 280 290 300 EGPRRLILKE QPTQLRLPEG CQGLAPGIEV TYRLQLHMLS CPCRAKATRT 310 320 330 340 350 LHEGKMPYLS GAAYNVAVIS ENQFGDGLNQ TWHIPADTHT EPVALNISVG 360 370 380 390 400 TNGTTMYWFA RAQSMIYCIE WQEVQDGGCL ATCSETAPQD PDPAGNATYE 410 420 430 440 450 NSRESCANGQ EWCYVITIFA SARPEKLTILW STVLSTYHFG GNASRACTPH 460 470 480 490 500 HVSVMNHSLD SVSVSWAPSL LSTCPGVLEK YVVRCDREDS HQVSEMPVQF 510 520 530 540 550 TETQVILSGL RAGVANTVQV PADTANLAGV WSQPQREKIE VQVSDWLIFF 560 570 580 590 600 ASLSSFLSIL LVGVLSYLGL NPAARNLCPP LPTPCASSAI EFPCKETWQ 610 620 630 640 650 WINFVDPQEE ASLQEALVVE MEWDKCEKTE FLEKTELPEG APRALSTEL 660 SLDGDRCKA KM

56	IL-12 p35 human (Uniprot accession no. P29459)	1020304050 MCHQQLVISW FSLVFLASPL VAIWELKKDV YVVELDWPDP APGEMVVLTC 60708090100 DTPEEDGITW TLDQSSEVLG SGKTLTIQVK EFGDAGQYTC HKGGEVLSHS 110120130140150 LLLLHKKEG IWSIDILKDQ KEPKNKTFLR CEAKNYSGRF TCWMLTTIST 160170180190200 DLTFSVKSSR GSSDPQGVTC GAATLSAERV RGDNKEYEVS VECQEDSACP 210220230240250 AAEESLPIEV MVDVHKLKY ENYTSSFFIR DIIKPPPKN LQLKPLKNSR 260270280290300 QVEVSWEYPD TWSTPHSYFS LTFCVQVQGK SKREKKDRVF TDKTSATVIC 310320 RKNASISVRA QDRYYSSSW5 EWASVPCS
57	IL-12 p40 mouse (Uniprot accession no. P43432)	1020304050 MCPQKLTISW FAIVLLVSPL MAMWELEKDV YVVEVDWTPD APGETVNLTC 60708090100 DTPEEDDITW TSDQRHGVIG SGKTLTITVK EFLDAGQYTC HKGGETLSHS 110120130140150 HLLLHKKEG IWSIEILKNF KNKTLFKCEA PNYSGRFTCS WLVRNMDLK 160170180190200 FNIKSSSSSP DSRVAVTCMA SLSAEKVTLD QRDYKYSVS CQEDVTCPTA 210220230240250 EETLPIELAL EARQONKYEN YSTSFFIRDI IKPDPKLNQ MKPLKNSQVE 260270280290300 VSWEYPDWS TPHSYFSLKF FVRIQRKKEK MKETEEGCNQ KGAFLEKTS 310320330 TEVQCKGGNV CVQAQDRYYN SSCSKWACVP CRVR5
58	ACP63 Anti-FN CGS-2 scFv	mdmrvpaqllgllllwlgarcEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCA RGVGAFRPYRKHEWGQGLTVTSRggggsgggsgggsgggsgSSELTQDPAVSVALGQTVRIT CQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQ AEDEADYYCNSSPFEHNLVVFVGGGKLTVLHHHHHHEPEA
59	ACP34 Mouse IL-12 fusion protein	mdmrvpaqllgllllwlgarcvrvsvsgparclsqsrnllktddmvktareklkhsctaedidheditrdqstlktclplelhkn esclatretsstrgscppqktslmmclclgsiyedlkmyqtefqainaqlnlnhqqiildkgmlvaidelmqslnhngetlrqk ppvgeadpyrvkmklcillhafstrvvtinrmgyllsaSGGPGPAGMKGLPGSmwelekdvyvvevdwtpdap getvnlctdteedditwtsdqrhgvisgsktltitvkefldagqytkhggetlshshllhkkengiwsteilknfkntflkceap nysgrftcswlvrnmdlkfniksssspsdravtcgmaslsaekvtdqrdyeykysvscqedvtcptaetlpielalearqqn yenystsfirdiikpdpknlnqmkplknsqvevswepdswstphsyfslkffvriqrkkekmketeegcnqkgaflektst evqckggnvcevqaqdryynsscskwacvprrvrsHHHHHH
60	ACP35	mdmrvpaqllgllllwlgarcvrvsvsgparclsqsrnllktddmvktareklkhsctaedidheditrdqstlktclplelhkn esclatretsstrgscppqktslmmclclgsiyedlkmyqtefqainaqlnlnhqqiildkgmlvaidelmqslnhngetlrqk

	Mouse IL-12 fusion protein	ppvgeadpyrvkmklcillhafstrvvtinrmvgyssagggsgggsgggsgSGGPGPAGMKGLPGSggggsg ggsgggggsmwelekdyvvvevdwtpdapgetvnlctdtpeddittwtsdqrhgvigsgkltitvkefldagqytchkggetl shshlllhhkengiwesteilkfnkntflkceapnysgrftcswlvrnmdlknfknksssspsdravtcgmaslsaekvtldqrdy ekysvscqedvtcptaetlpielalearqqnkyenystsfirdiikpdpknqlmqmplknsqvevswepdswstphsyfslk ffvriqrkkekmketeegcnqkgafvektstevqckggncvqvaaqdrynsscskwacvpcrvrsHHHHHH
61	ACP36 Mouse IL-12 fusion protein	mdmrvpaqllgllllwlgarcEVQLVESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQAP GKGLEWVSSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNSLRPEDTAVYYCTI GGSLSVSSQGTLLTVSSSGGPGPAGMKGLPGSsmwelekdyvvvevdwtpdapgetvnlctdtpedd itwtsdqrhgvigsgkltitvkefldagqytchkggetlshshlllhhkengiwesteilkfnkntflkceapnysgrftcswlvrn mdlknfknksssspsdravtcgmaslsaekvtldqrdyeykysvscqedvtcptaetlpielalearqqnkyenystsfirdiikp ppknqlmqmplknsqvevswepdswstphsyfslkffvriqrkkekmketeegcnqkgafvektstevqckggncvqvaaq drynsscskwacvpcrvrsggggsgggsgggsgsrvipvsparclsqsrnllktddmvktareklkhysctaedidheditr dqtstlktclplelhknesclatretsstrgscppqktslmmtlclgsiyedlkmyqtefqainaalnqhnhqqiildkgmlvaide lmqslnhngetlrqkppvgeadpyrvkmklcillhafstrvvtinrmvgyssaSGGPGPAGMKGLPGSEVQLV ESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQAPGKGLEWVSSISGSGRDTLYA ESVKGRFTISRDNAAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSSQGTLLTVSSHHH HHH
62	ACP37 Mouse IL-12 fusion protein	mdmrvpaqllgllllwlgarcQVQLQESGGGLVQAGGSLRSLCAASGRIFSIDIMSWYRQAPG KQRELVARITRGGTISYDDSVKGRFTISRDNAAKTTLYLQMNSLRPEDTGYYCNAL YGTDYWGKGTQVTVSSggggsgggsgggsgEVQLVESGGGLVQPGNSLRSLCAASGFTF SKFGMSWVRQAPGKGLEWVSSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNS LRPEDTAVYYCTIGGSLSVSSQGTLLTVSSSGGPGPAGMKGLPGSsmwelekdyvvvevdw pdapgetvnlctdtpeddittwtsdqrhgvigsgkltitvkefldagqytchkggetlshshlllhhkengiwesteilkfnkntflk ceapnysgrftcswlvrnmdlknfknksssspsdravtcgmaslsaekvtldqrdyeykysvscqedvtcptaetlpielalearq qnkyenystsfirdiikpdpknqlmqmplknsqvevswepdswstphsyfslkffvriqrkkekmketeegcnqkgafve ktstevqckggncvqvaaqdrynsscskwacvpcrvrsggggsgggsgggsgsrvipvsparclsqsrnllktddmvktare klkhysctaedidheditr dqtstlktclplelhknesclatretsstrgscppqktslmmtlclgsiyedlkmyqtefqainaaln hnhqqiildkgmlvaide lmqslnhngetlrqkppvgeadpyrvkmklcillhafstrvvtinrmvgyssaSGGPGPAG MKGLPGSEVQLVESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQAPGKGLEWV SSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSS QGTLLTVSSHHHHHHH
63	ACP79 Mouse IL-12 fusion protein	mdmrvpaqllgllllwlgarcQVQLQESGGGLVQAGGSLRSLCAASGRIFSIDIMSWYRQAPG KQRELVARITRGGTISYDDSVKGRFTISRDNAAKTTLYLQMNSLRPEDTGYYCNAL YGTDYWGKGTQVTVSSggggsgggsgggsgEVQLVESGGGLVQPGNSLRSLCAASGFTF SKFGMSWVRQAPGKGLEWVSSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNS LRPEDTAVYYCTIGGSLSVSSQGTLLTVSSSGGPGPAGMKGLPGSsmwelekdyvvvevdw pdapgetvnlctdtpeddittwtsdqrhgvigsgkltitvkefldagqytchkggetlshshlllhhkengiwesteilkfnkntflk ceapnysgrftcswlvrnmdlknfknksssspsdravtcgmaslsaekvtldqrdyeykysvscqedvtcptaetlpielalearq qnkyenystsfirdiikpdpknqlmqmplknsqvevswepdswstphsyfslkffvriqrkkekmketeegcnqkgafve ktstevqckggncvqvaaqdrynsscskwacvpcrvrsggggsgggsgggsgsrvipvsparclsqsrnllktddmvktare klkhysctaedidheditr dqtstlktclplelhknesclatretsstrgscppqktslmmtlclgsiyedlkmyqtefqainaaln hnhqqiildkgmlvaide lmqslnhngetlrqkppvgeadpyrvkmklcillhafstrvvtinrmvgyssaSGGPGPAG MKGLPGSEVQLVESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQAPGKGLEWV SSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSS QGTLLTVSSHHHHHHH
64	ACP80 Mouse IL-12 fusion protein	mdmrvpaqllgllllwlgarcEVQLVESGGGLVQPGNSLRSLCAASGFTFSKFGMSWVRQAP GKGLEWVSSISGSGRDTLYAESVKGRFTISRDNAAKTTLYLQMNSLRPEDTAVYYCTI GGSLSVSSQGTLLTVSSSGGPGPAGMKGLPGSsmwelekdyvvvevdwtpdapgetvnlctdtpedd itwtsdqrhgvigsgkltitvkefldagqytchkggetlshshlllhhkengiwesteilkfnkntflkceapnysgrftcswlvrn mdlknfknksssspsdravtcgmaslsaekvtldqrdyeykysvscqedvtcptaetlpielalearqqnkyenystsfirdiikp ppknqlmqmplknsqvevswepdswstphsyfslkffvriqrkkekmketeegcnqkgafvektstevqckggncvqvaaq drynsscskwacvpcrvrsggggsgggsgggsgsrvipvsparclsqsrnllktddmvktareklkhysctaedidheditr dqtstlktclplelhknesclatretsstrgscppqktslmmtlclgsiyedlkmyqtefqainaalnqhnhqqiildkgmlvaide

[illegible]

	fusion protein	asvpcsgggsgggsgggsgggsvipvsgparclsqsrnllkttddmvktareklkhsyctaedidheditrqstlktclplelhnk essclatretsstrgscldppqktslmmmtclglsiyedlkmyqtefqainaalqnhnhqqiildkgmlvaidelmqslnhngetlrqk ppvgeadpyrvkmklcillhafstrvvtinrvmgylssaSGGPGPAGMKGLPGSgggsgggsgggsgggsgggsgg ggsgggsggsQSVLTQPPSVSGAPGQRVTISCSGSRNIGSNTVKWYQQLPGTAPKLLIYY NDQRPSGV PDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDRYTHPALLFGTGTKV TVLgggsgggsgggsgggsgVQVQVLESGGGVVQGRSLRLSCAASGFTFSSYGMHWVRQAPG KGLEWVAFIRYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCK THGSHDNWGQGTMTVTVSSgggsgggsgggsgggsgEVQVLESGGGLVQPGNSLRLSCAASGF TFSKFGMSWVRQAPGKGLEWVSSISGSGRDTLYAESVKGRFTISRDN AKTTLYLQM NSLRPEDTAVYYCTIGGSLSVSSQGT LVTVSSHHHHHHEPEA
69	ACPI40 Chimeric IL-12 fusion protein	mdmrvpaqllgllllwlgarcQVQLQESGGGLAQAGGSLRLSCAASGFTVSNVMAWYRQTP GKQREFVAIINSVGSTNYADSVKGRFTISRDN AKNTVYLQMN NLKPEDTAVYYVCNR NFDRIYWGQGTQVTVSSSGGPGPAGMKGLPGSiwelkkdvyyveldwypdagemvvltdtpeed gitwtldqssevlsgsklttiqvkfegdagqytchkggevlshsllllhhkkedgiwstdilkdqpeknkftlrceaknysgrftew wlttistdltfsvksrsgssdpqgvtcgaatlsaervrgdnkeyeysvecqedsacpaaeeslpievmdavhklkyenytsffir diikpdpknqlklpklnsrqvevsweypdtwstphsyfsltfcvqvqgkskrekkdrvftdksatvicrk nasisvraqdryys sswsewasvpcsgggsgggsgggsgggsvipvsgparclsqsrnllkttddmvktareklkhsyctaedidheditrqstlktc lplelhnknesclatretsstrgscldppqktslmmmtclglsiyedlkmyqtefqainaalqnhnhqqiildkgmlvaidelmqslnh ngetlrqkppvgeadpyrvkmklcillhafstrvvtinrvmgylssaSGGPGPAGMKGLPGSgggsgggsgggsgggsgg sgggsgggsgggsgggsgQSVLTQPPSVSGAPGQRVTISCSGSRNIGSNTVKWYQQLPGTAPK LLIYYNDQRPSGV PDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDRYTHPALLFG TGTKVTVLgggsgggsgggsgggsgVQVQVLESGGGVVQGRSLRLSCAASGFTFSSYGMHWV RQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAV YYCKTHGSHDNWGQGTMTVTVSSgggsgggsgggsgggsgEVQVLESGGGLVQPGNSLRLSC AASGFTFSKFGMSWVRQAPGKGLEWVSSISGSGRDTLYAESVKGRFTISRDN AKTTL YLQMN SLRPEDTAVYYCTIGGSLSVSSQGT LVTVSSHHHHHHEPEA
70	ACPI17 Anti-FN CGS-2 scFv	mdmrvpaqllgllllwlgarcEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCA RGVGAFRPYRKHEWGQGT LVTVSRgggsgggsgggsgggsgSSELTQDPAVSVALGQTVRIT CQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTTTGAQ AEDEADYYCNSSPFEHNLVVFGGGTKLTVLHHHHHHEPEA
71	EGFR (G8) Prodrug C1486	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQGGGGGLDGN EEPGGLE WVSSISGSGRDTLYADSVKGRFTISRDN AKTTLYLQMN SLRPEDTAVYYCTIGGSL SVSSQGT LVTVSSGGGGKPLGLQARVVGGGGTQT VVTQEPSLTVSPGGTVTLTCASST GAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTL SGVQP EDEAEYYCTLWYSNRWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLV QPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVK DRFTISRDDSKNTAYLQMN NLKTEDTAVYYCVRHANFGNSYISYWAYWGQGT LVT VSSGGGGSGGGSEVQLVESGGGLVQPGGSLTLSCAASGRTFSSYAMGWFRQAPG KERE FVAINWASGSTYYADSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAAGYQINSGNYN FKDYEYDYWGQGT LVTVSSHHHHHH
72	EGFR (G8) Non- cleavable	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQGGGGGLDGN EEPGGLE WVSSISGSGRDTLYADSVKGRFTISRDN AKTTLYLQMN SLRPEDTAVYYCTIGGSL SVSSQGT LVTVSSGGGGSGGGGSGGVVGGGGTQT VVTQEPSLTVSPGGTVTLTCASS TGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTL SGVQ PEDEAEYYCTLWYSNRWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLV

	Prodrug C1756	QPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVK DRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQGLTVT VSSGGGGSGGGSEVQLVESGGGLVQPGGSLTLSCAASGRTFSSYAMGWFRQAPGKEREFF VVAINWASGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAGYQINSGNYN FKDYEYDYWGQGLTVTVSSH HHHHHH
73	EGFR (G8) Active Drug C1300	<u>VVGGGGTQTVVTQEPSLTVSPGGTVTLTCASSTGAVTSGNYPNWVQKPGQAPRGL</u> IGGTKFLVPGTPARFSGSLLGGKAALTL SGVQPEDEAEYYCTLWYSNRWVFGGGTK LTVLGGGGSGGGSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWV RQAPGKGLEWVARIRSKYNNYATYYADQVKDRFTISRDDSKNTAYLQMNNLKTED TAVYYCVRHANFGNSYISYWAYWGQGLTVTVSSGGGGSGGGSEVQLVESGGGLVQ <u>PGGSLTLSCAASGRTFSSYAMGWFRQAPGKEREFF</u> VVAINWASGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAGYQINSGNYNFKDYEYDYWGQGLTVTVSSH HHHHHH
74	PSMA Prodrug C1872	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQGGGGGLDGNEEPGGLE WVSSISGSGRDTLYADSVKGRFTISRDN AKTTLYLQMNSLRPEDTAVYYCTIGGSL VSSQGLTVTVSSGGGGKPLGLQARVVGGGGTQTVVTQEPSLTVSPGGTVTLTCASST GAVTSGNYPNWVQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTL SGVQP EDEAEYYCTLWYSNRWVFGGGTKLTVLGGGGSGGGSGGGGSEVQLVESGGGLV QPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVK DRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQGLTVT VSSGGGGSGGGSEVQLVESGGGLVQPGGSLTLSCAASRFMISEYHMHWWVRQAPGKGLE WVSTINPAGTTDYAESVKGRFTISRDN AKNTLYLQMNSLKPEDTAVYYCDSYGYRGQGTQ VTVSSH HHHHHH
75	PSMA Non- cleavable Prodrug C1873	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQGGGGGLDGNEEPGGLE WVSSISGSGRDTLYADSVKGRFTISRDN AKTTLYLQMNSLRPEDTAVYYCTIGGSL VSSQGLTVTVSSGGGGSGGGSGGVVGGGGTQTVVTQEPSLTVSPGGTVTLTCASS TGAVTSGNYPNWVQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTL SGVQ PEDEAEYYCTLWYSNRWVFGGGTKLTVLGGGGSGGGSGGGGSEVQLVESGGGLV QPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVK DRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQGLTVT VSSGGGGSGGGSEVQLVESGGGLVQPGGSLTLSCAASRFMISEYHMHWWVRQAPGKGLE WVSTINPAGTTDYAESVKGRFTISRDN AKNTLYLQMNSLKPEDTAVYYCDSYGYRGQGTQ VTVSSH HHHHHH
76	PSMA Active Drug C1875	<u>VVGGGGTQTVVTQEPSLTVSPGGTVTLTCASSTGAVTSGNYPNWVQKPGQAPRGL</u> IGGTKFLVPGTPARFSGSLLGGKAALTL SGVQPEDEAEYYCTLWYSNRWVFGGGTK LTVLGGGGSGGGSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWV RQAPGKGLEWVARIRSKYNNYATYYADQVKDRFTISRDDSKNTAYLQMNNLKTED

		TAVYYCVRHANFGNSYISYWAYWGQGTTLTVSSGGGGSGGGSEVQLVESGGGLVQ PGGSLTLSCAASRFMISEYHMHVVRQAPGKGLEWVSTINPAGTTDYAESVKGRFTISRDN AKNTLYLQMNSLKPEDTAVYYCDSYGYRGQGTQVTVSSHHHHHH
77	GFP TriTAC C646	QVQLVESGGALVQPGGSLRLSCAASGFPVNRYSMRWYRQAPGKEREWVAGMSSAGDRSS YEDSVKGRFTISRDDARNTVYLQMNSLKPEDTAVYYCNVNVGFYWGQGTQVTVSSGGG GSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGRDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSSQG TLTVVSSGGGGSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWVRQA PGKGLEWVARIRSKYNNYATYYADQVKDRFTISRDDSKNTAYLQMNNLKTEDTAV YYCVRHANFGNSYISYWAYWGQGTTLTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCASSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPGTPARFSGS LLGGKAALTLSGVQPEDEAEYYCTLWYSNRWVFGGGTKLTVLHHHHHH
78	non- masked/n on- cleavable TriTAC C1874	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSSISGSGR DTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSSQGTLTV SSGGGGSGGGGSGGVVGGGGTQTVVTQEPSLTVSPGGTVTLTCASSTGAVTSGNYP NWVQQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCT LWYSNRWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLKLSC AASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVKDRFTISRDDS KNTAYLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQGTTLTVSSGGGGSG GGSEVQLVESGGGLVQPGGSLTLSCAASRFMISEYHMHVVRQAPGKGLEWVSTINP AGTTDYAESVKGRFTISRDNAKNTLYLQMNSLKPEDTAVYYCDSYGYRGQGTQVT VSSHHHHHH
79	Blocker 12 (IL-12 blocker)	mdmrvpaqlglillwlgarcQSVLTQPPSVSGAPGQRVTISCSGSRNIGSNTVKWYQQLPGTAPKLLIYND QRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDRYTHPALLFGTGKVTVLggggsgggsggggs QVQLVESGGGVVQPGSLRLSCAASGFTFSSYGMHVVVRQAPGKGLEWVAFIRYDGSNKYYADSVKGR FTISRDNKNTLYLQMNSLRAEDTAVYYCKTHGSHDNWGQGTMTVSSHHHHHH

INCORPORATION BY REFERENCE

[196] The entire disclosures of all patent and non-patent publications cited herein are each incorporated by reference in their entireties for all purposes.

OTHER EMBODIMENTS

[197] The disclosure set forth above may encompass multiple distinct inventions with independent utility. Although each of these inventions has been disclosed in its preferred form(s), the specific embodiments thereof as disclosed and illustrated herein are not to be considered in a limiting sense,

because numerous variations are possible. The subject matter of the inventions includes all novel and nonobvious combinations and subcombinations of the various elements, features, functions, and/or properties disclosed herein. The following claims particularly point out certain combinations and subcombinations regarded as novel and nonobvious. Inventions embodied in other combinations and subcombinations of features, functions, elements, and/or properties may be claimed in this application, in applications claiming priority from this application, or in related applications. Such claims, whether directed to a different invention or to the same invention, and whether broader, narrower, equal, or different in scope in comparison to the original claims, also are regarded as included within the subject matter of the inventions of the present disclosure.

CLAIMS

1. A fusion polypeptide of the formula:

[A]-[L1]-[D]-[L2]-[B] or [B]-[L1]-[A]-[L1]-[D]

wherein,

A is an interleukin 12 (IL-12) polypeptide;

B is a half-life extension element, wherein the half-life extension element is human serum albumin or an antigen-binding polypeptide that binds human serum albumin;

L1 is a protease-cleavable polypeptide linker, L2 is polypeptide linker that is optionally protease-cleavable, and when protease-cleavable L2 comprises at least one sequence that is cleavable by a protease, wherein for each of L1 and L2, independently, the protease is selected from the group consisting of a kallikrein, thrombin, chymase, carboxypeptidase A, an elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), a fibroblast activation protein (FAP), an ADAM metalloproteinase, a plasminogen activator, a cathepsin, a caspase, a tryptase, and a tumor cell surface protease; and

D is an IL-12 blocking moiety, wherein the blocking moiety is an antibody or antigen-binding fragment of an antibody that binds the IL-12 polypeptide; and wherein

the fusion polypeptide has attenuated IL-12 receptor activating activity, wherein the IL-12-receptor activating activity of the fusion polypeptide is at least about 10 fold less than the IL-12-receptor activating activity of the polypeptide that comprises the IL-12 polypeptide that is produced by cleavage of the protease-cleavable polypeptide linker L1 or, when L2 is protease-cleavable, by cleavage of both L1 and L2, and wherein the IL-12-receptor activating activity is assessed using a HEK Blue reporter cell assay, with equal amounts on a mole basis of the IL-12 polypeptide and the fusion polypeptide.

2. The fusion polypeptide of claim 1, wherein [A] has the formula:

[A1]-[L3]-[A2] or [A2]-[L3]-[A1], wherein

A1 is an IL-12 p40 subunit polypeptide;

A2 is an IL-12 p35 subunit polypeptide; and

L3 is a polypeptide linker that is optionally protease cleavable.

3. The fusion polypeptide of claim 1 or claim 2, wherein the IL-12 blocking moiety comprises a single domain antibody, Fab or scFv that binds the IL-12 polypeptide.
4. The fusion polypeptide of any one of the preceding claims, wherein L2 is a protease-cleavable linker.
5. The fusion polypeptide of any one of the preceding claims, wherein L1 is a substrate for a first protease and L2 is a substrate for a second protease.
6. The fusion polypeptide of any one of the preceding claims, wherein each protease-cleavable polypeptide independently comprises two or more cleavage sites for the same protease, or two or more cleavage sites that are cleaved by different proteases or at least one of the protease-cleavable polypeptides comprises a cleavage site for two or more different proteases.
7. The fusion polypeptide of any one of the preceding claims, wherein the IL-12 blocking moiety inhibits activation of the IL-12 receptor by the fusion polypeptide.
8. The fusion polypeptide of any one of the preceding claims, wherein the cathepsin is cathepsin B, cathepsin C, cathepsin D, cathepsin E, cathepsin K, cathepsin L, or cathepsin G.
9. The fusion polypeptide of any one of claims 1-7, wherein the matrix metalloprotease (MMP) is MMP1, MMP2, MMP3, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, or MMP14.
10. A nucleic acid encoding the polypeptide of any one of the preceding claims.
11. An isolated vector comprising the nucleic acid of claim 10.

12. An isolated host cell comprising the vector of claim 11.
13. A method of making a pharmaceutical composition, comprising culturing the host cell of claim 12 under suitable conditions for expression and collection of desired polypeptides.
14. A pharmaceutical composition comprising i) an effective amount of the fusion polypeptide of any one of claims 1-9, and ii) a pharmaceutically acceptable excipient.
15. A pharmaceutical composition comprising at least one of each of:
 - a) a human interleukin 12 (IL-12) polypeptide comprising an IL-12 subunit polypeptide selected from IL-12p35 and IL-12p40;
 - b) an IL-12 blocking moiety, wherein the IL-12 blocking moiety comprises a ligand-binding domain or fragment of a cognate receptor for the IL-12 polypeptide, or an antibody or antigen-binding fragment of an antibody that binds the IL-12 polypeptide;
 - c) a protease-cleavable polypeptide linker; and
 - d) a half-life extension element wherein the half-life extension element is human serum albumin, an antigen-binding polypeptide that binds human serum albumin, or an immunoglobulin Fc;wherein the IL-12 subunit polypeptide and the IL-12 blocking moiety are operably linked by the protease-cleavable polypeptide linker, the IL-12 polypeptide has attenuated IL-12-receptor activating activity at least about 10 fold less than the IL-12-receptor activating activity of the polypeptide that comprises the IL-12 polypeptide that is produced by cleavage of the protease-cleavable polypeptide linker, and wherein the IL-12 receptor activating activity is assessed using a HEK Blue reporter cell assay, with equal amounts on a mole basis of the IL-12 polypeptide and the pharmaceutical composition.
16. The pharmaceutical composition of claim 15, wherein the half-life extension element is operably linked to IL-12p35.

17. The pharmaceutical composition of claim 15 or claim 16, wherein the half-life extension element is operably linked to IL-12p40.
18. The pharmaceutical composition of any one of claims 15-17, comprising a first polypeptide comprising at least one of each of: a) a human interleukin 12 (IL-12) subunit polypeptide selected from IL-12p35 and IL-12p40; b) an IL-12 blocking moiety; and c) a protease-cleavable polypeptide linker, wherein the IL-12 subunit polypeptide and the IL-12 blocking moiety are operably linked by the protease-cleavable polypeptide linker.
19. The pharmaceutical composition of any one of claims 15-17, comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises at least one of each of: a) a human interleukin 12 (IL-12) subunit polypeptide selected from IL-12p35 and IL-12p40; b) an IL-12 blocking moiety; and c) a protease-cleavable polypeptide linker, wherein the IL-12 subunit polypeptide and the IL-12 blocking moiety are operably linked by the protease-cleavable polypeptide linker; and wherein the second polypeptide comprises a human interleukin 12 (IL-12) subunit polypeptide selected from IL-12p35 and IL-12p40.
20. The pharmaceutical composition of any one of claims 15-19, further comprising a tumor-specific antigen binding peptide.
21. The pharmaceutical composition of any one of claims 15-17 and 20, comprising a human IL-12p35 subunit polypeptide and a human IL-12p40 subunit polypeptide.
22. The pharmaceutical composition of any one of claims 15-21, wherein the protease-cleavable polypeptide linker comprises at least one sequence that is capable of being cleaved by a protease selected from the group consisting of a kallikrein, thrombin, chymase, carboxypeptidase A, cathepsin G, cathepsin L, an elastase, PR-3, granzyme M, a calpain, a matrix metalloproteinase (MMP), a

fibroblast activation protein (FAP), an ADAM metalloproteinase, a plasminogen activator, a cathepsin, a caspase, a tryptase, and a tumor cell surface protease.

23. The pharmaceutical composition of any one of claims 15-21, wherein IL-12 blocking moiety inhibits activation of the IL-12 receptor by the human IL-12 polypeptide.

24. The pharmaceutical composition of any one of claims 15-21, wherein the antibody fragment that binds to IL-12 is a single domain antibody, Fab or scFv.

25. The pharmaceutical composition of any one of claims 15-24, wherein the IL-12 polypeptide comprises a naturally-occurring IL-12 polypeptide sequence or a functional fragment thereof.

26. The pharmaceutical composition of any one of claims 15-25, wherein the protease cleavable polypeptide linker comprises a sequence that is cleaved by cathepsin selected from the group consisting of cathepsin B, cathepsin C, cathepsin D, cathepsin E, cathepsin K, cathepsin L, and cathepsin G.

27. The pharmaceutical composition of any one of claims 15-25, wherein the protease cleavable polypeptide linker comprises a sequence that is cleaved by a matrix metalloprotease (MMP) is selected from the group consisting of MMP1, MMP2, MMP3, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, and MMP14.

28. The pharmaceutical composition of any one of claims 15-27, wherein the serum half-life of the IL-12 polypeptide that is produced by cleavage of the protease-cleavable polypeptide linker is comparable to the half-life of naturally occurring IL-12.

29. The pharmaceutical composition of any one of claims 15-28, wherein the IL-12 polypeptide that is produced by cleavage if the protease-cleavable polypeptide linker does not comprise the half-life extension element or IL-12 blocking moiety.
30. The pharmaceutical composition of any one of claims 15-29, wherein the cognate receptor for the IL-12 is IL-12R beta 1 (IL-12R β 1) or IL12R beta 2 (IL-12R β 2).

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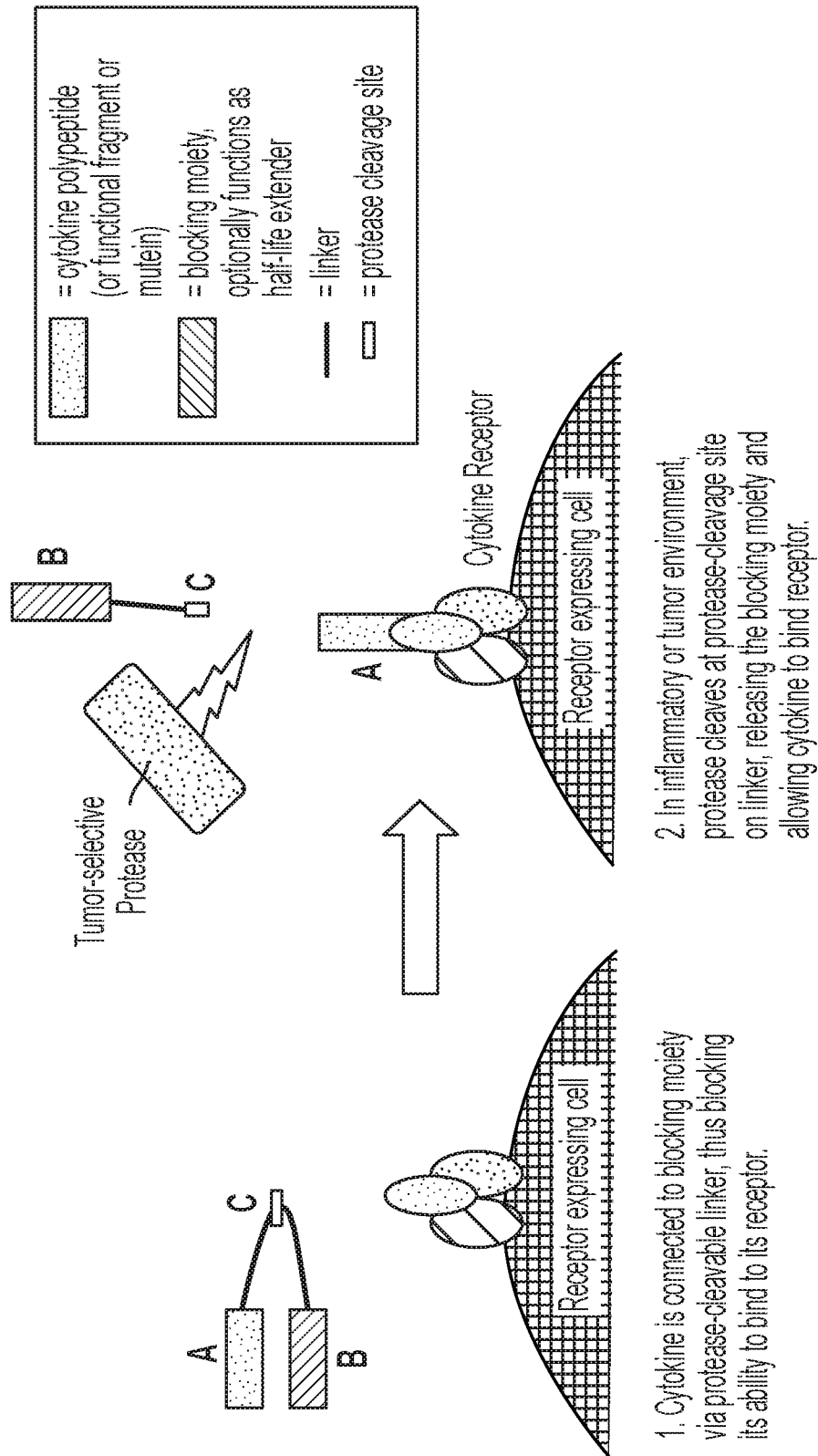


FIG. 1a

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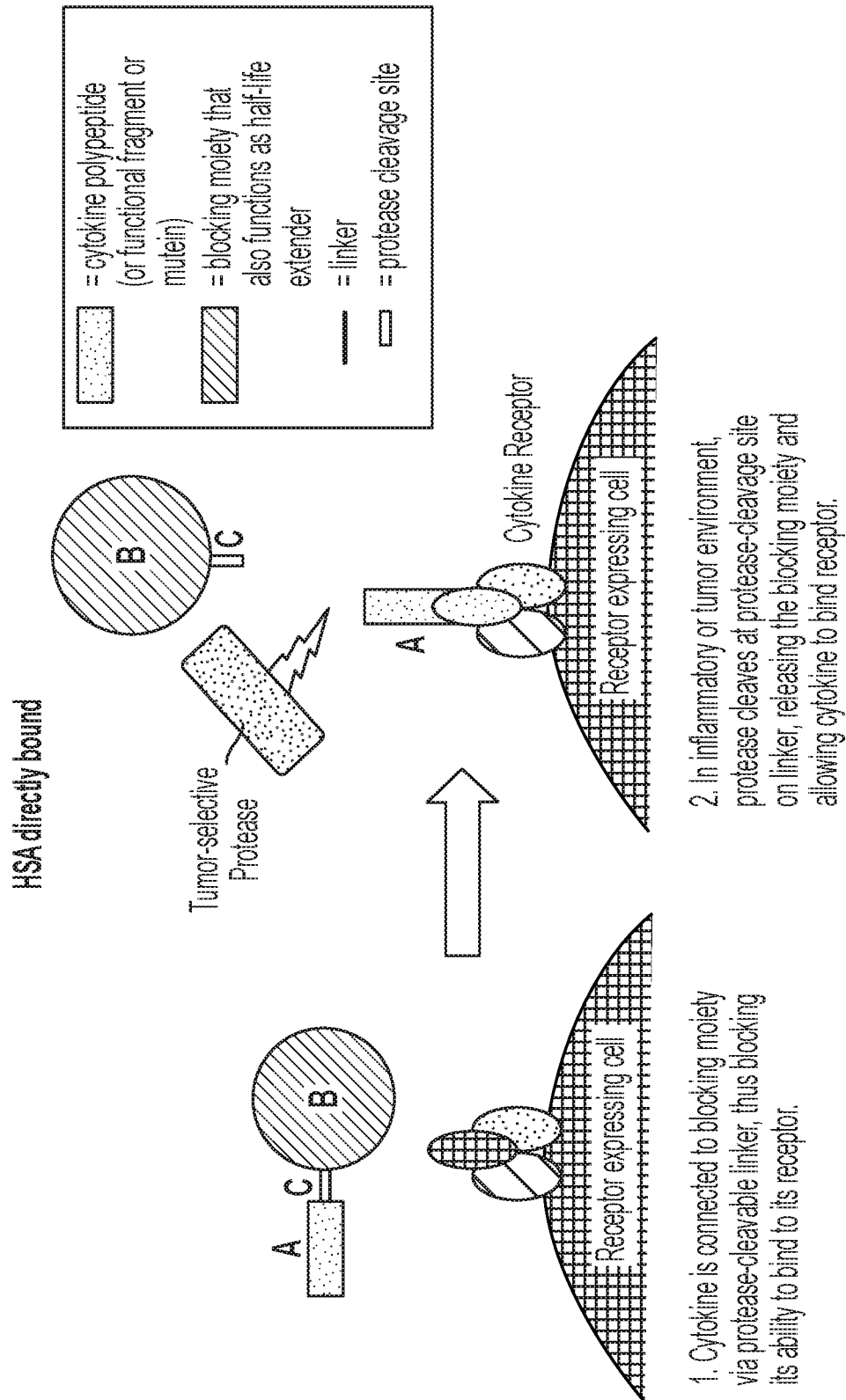
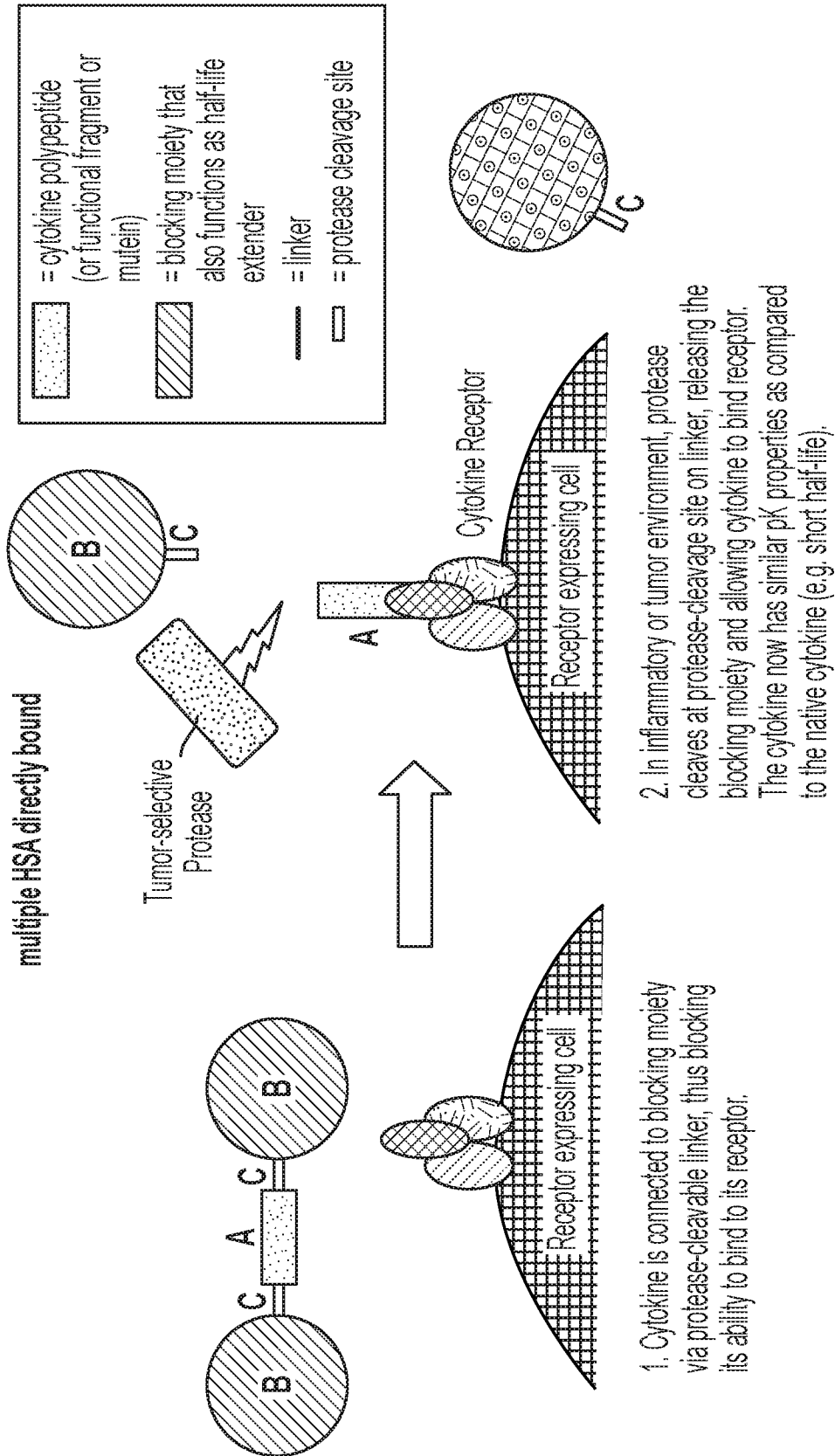


FIG. 1b

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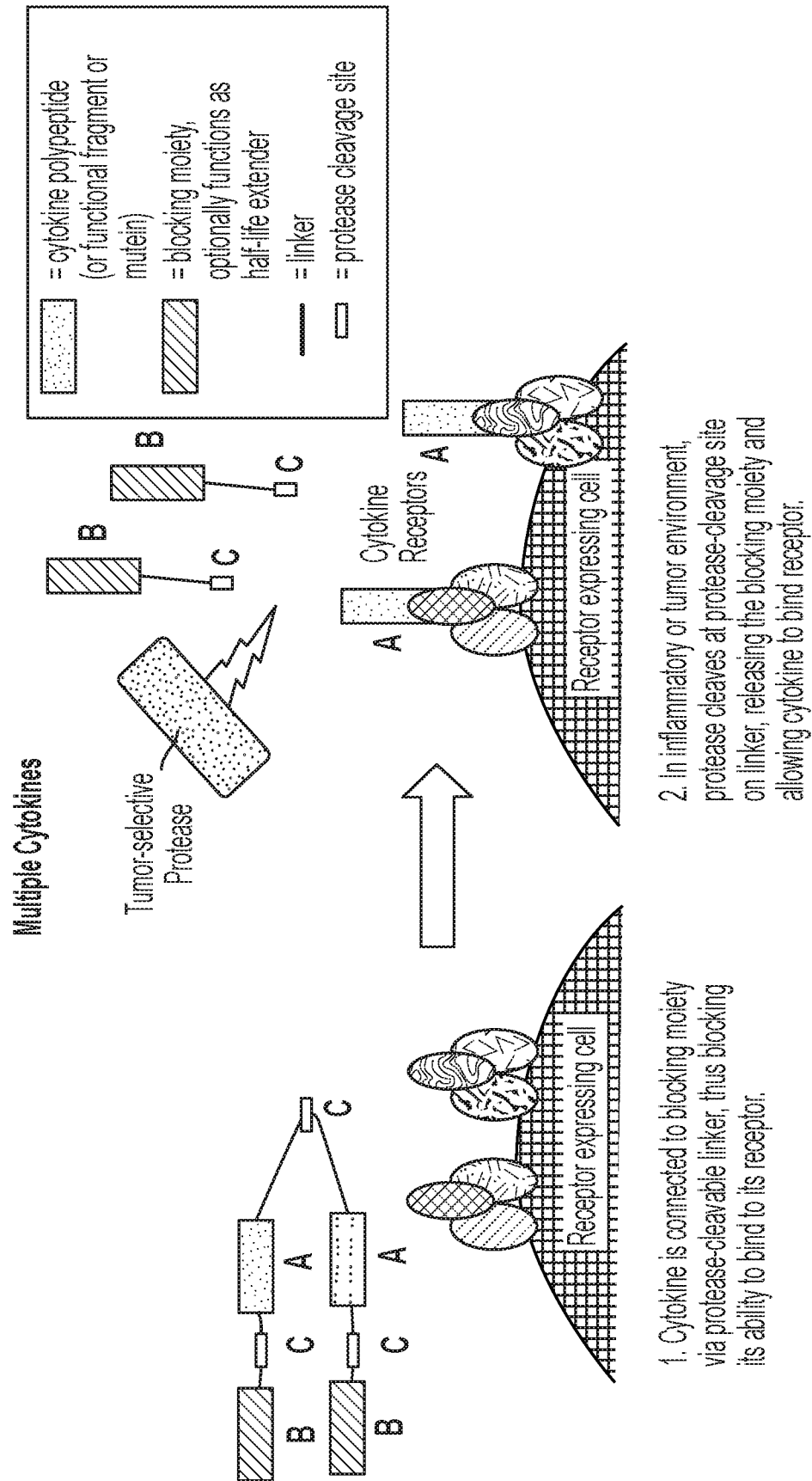


FIG. 1d

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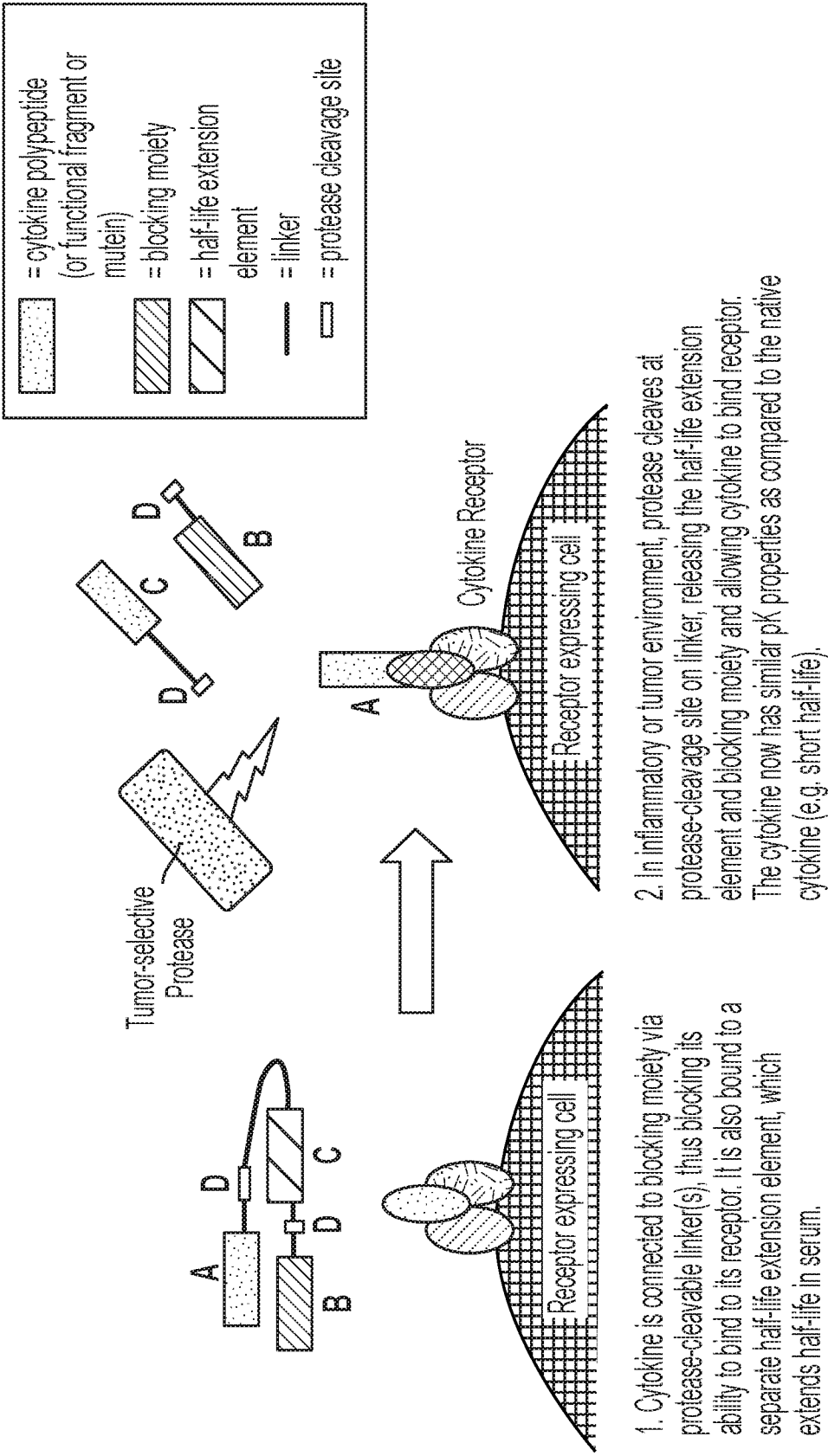


FIG. 2

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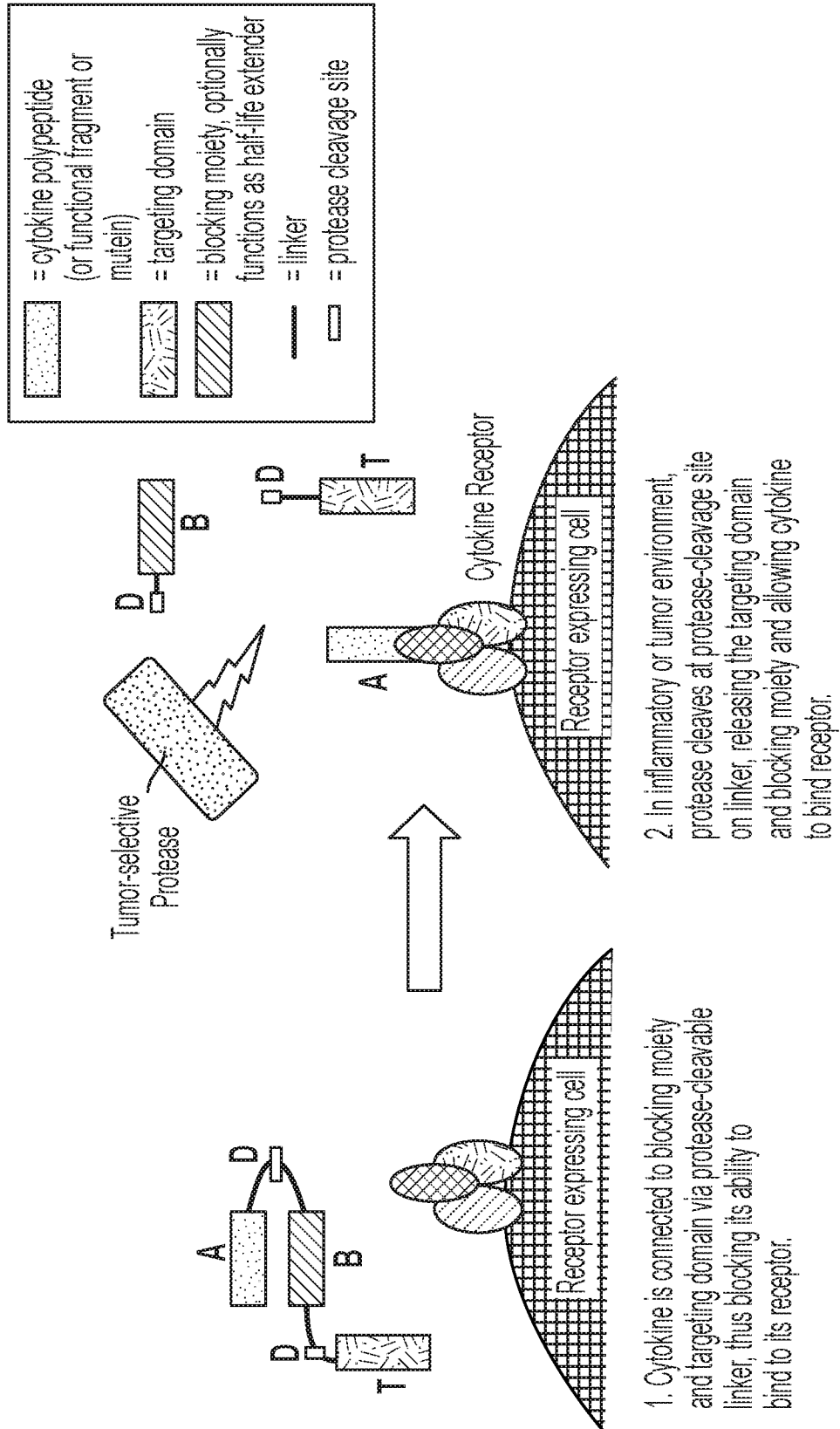


FIG. 3

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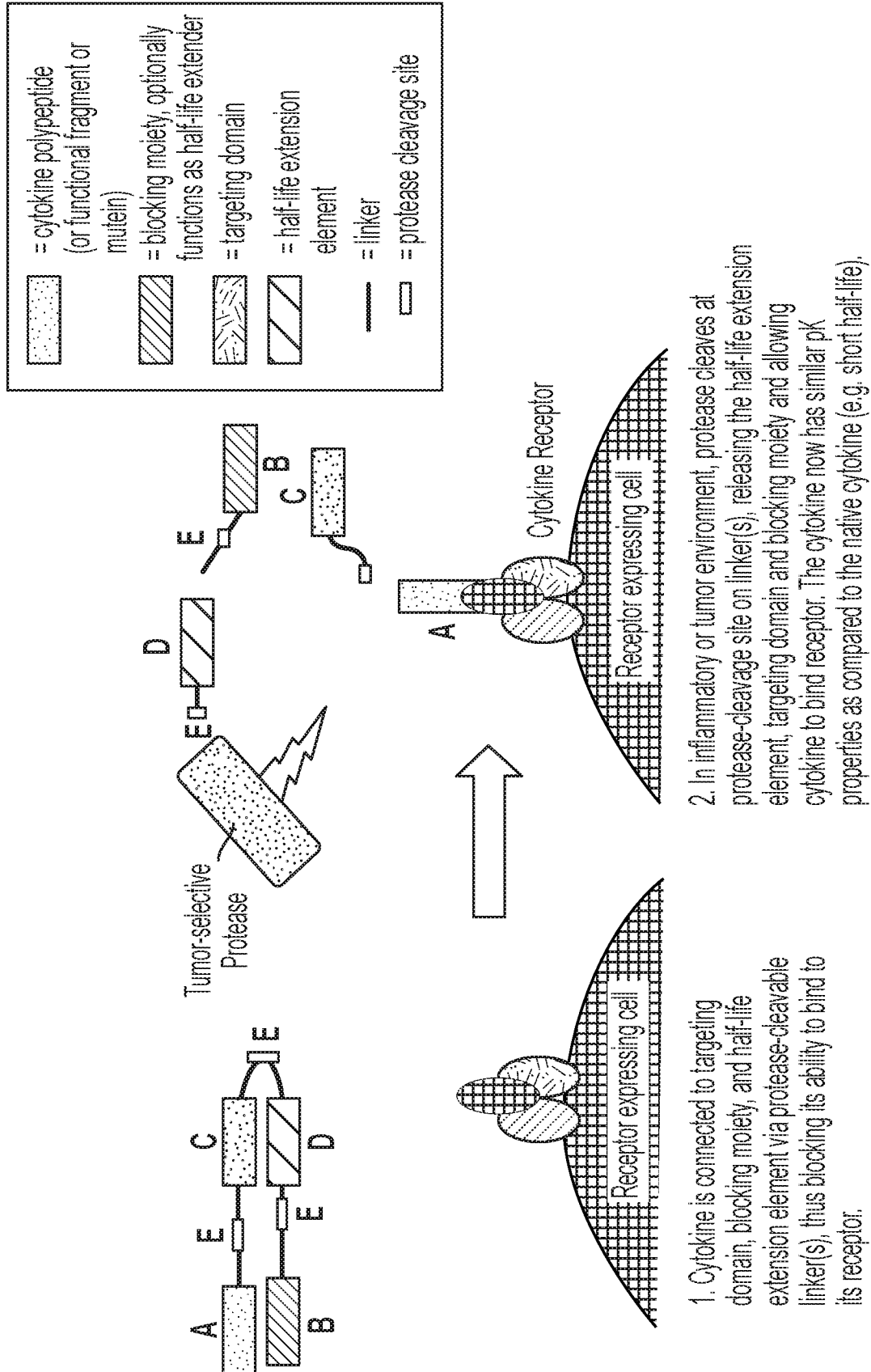


FIG. 4a

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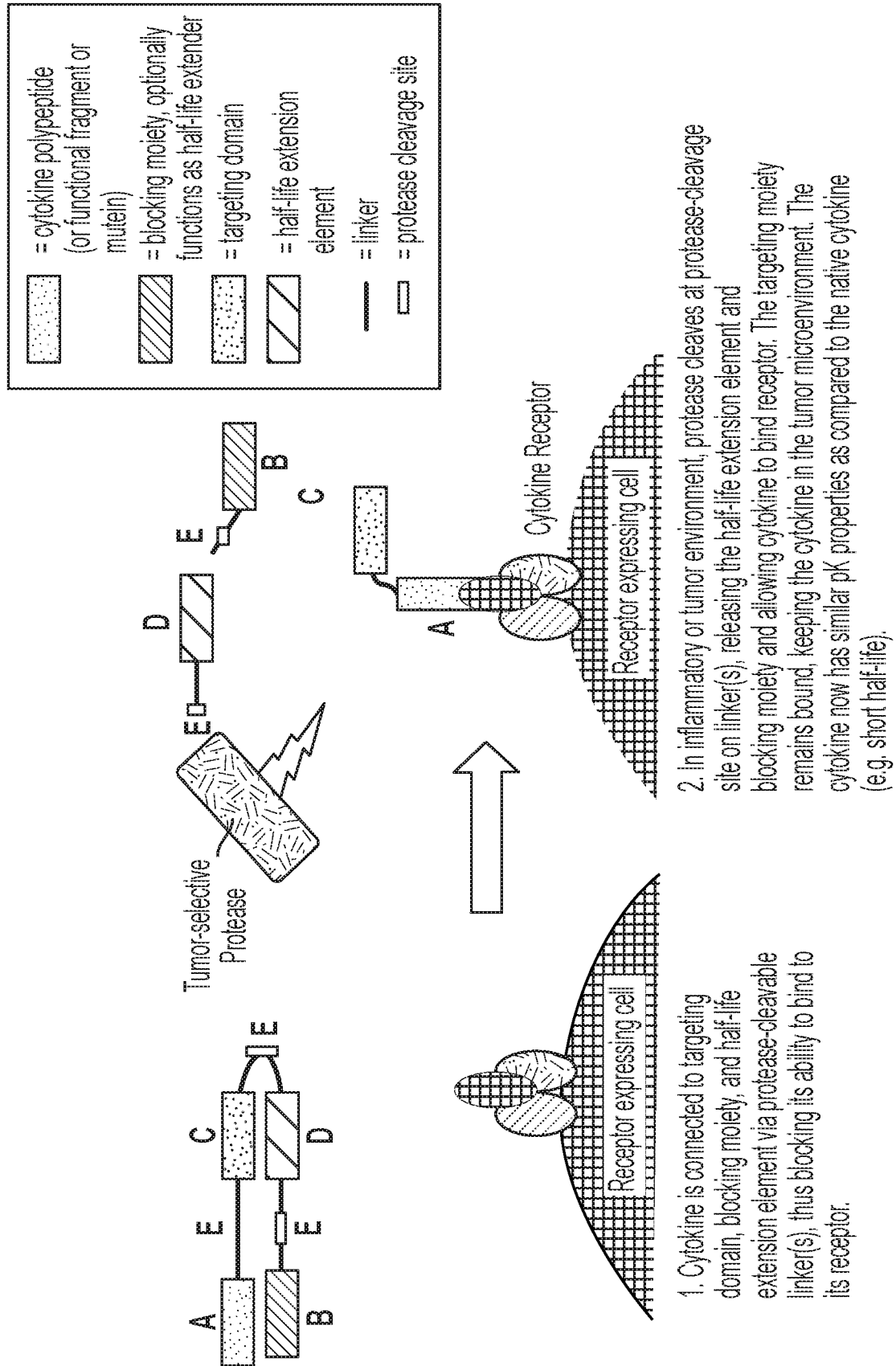


FIG. 4b

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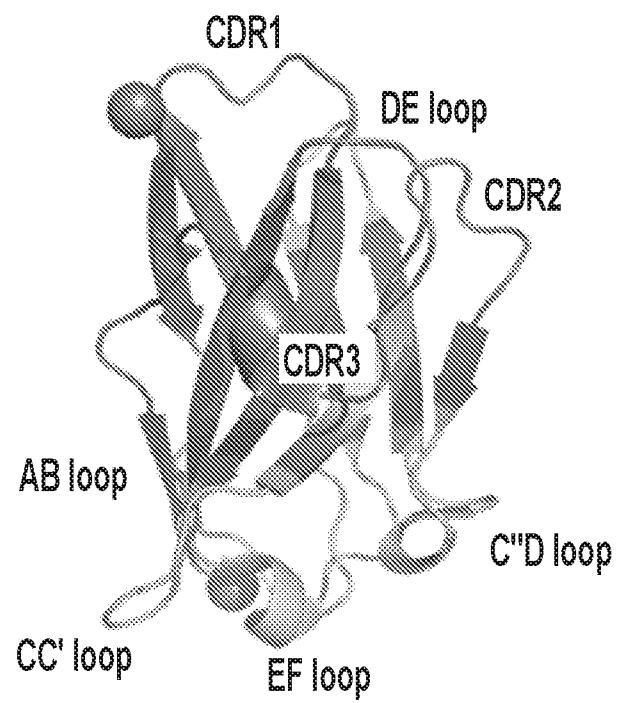


FIG. 5

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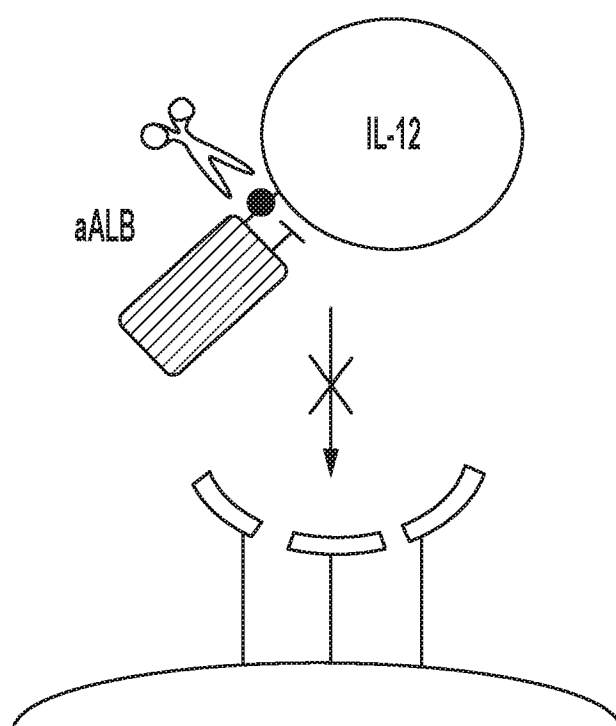


FIG. 6

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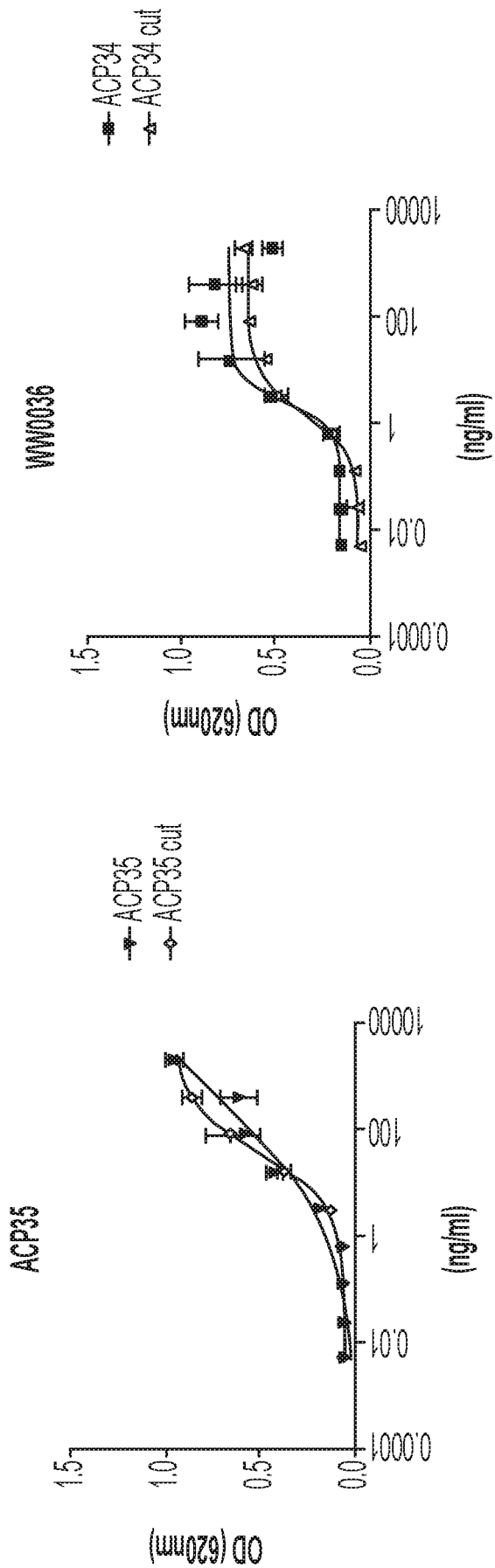


FIG. 7

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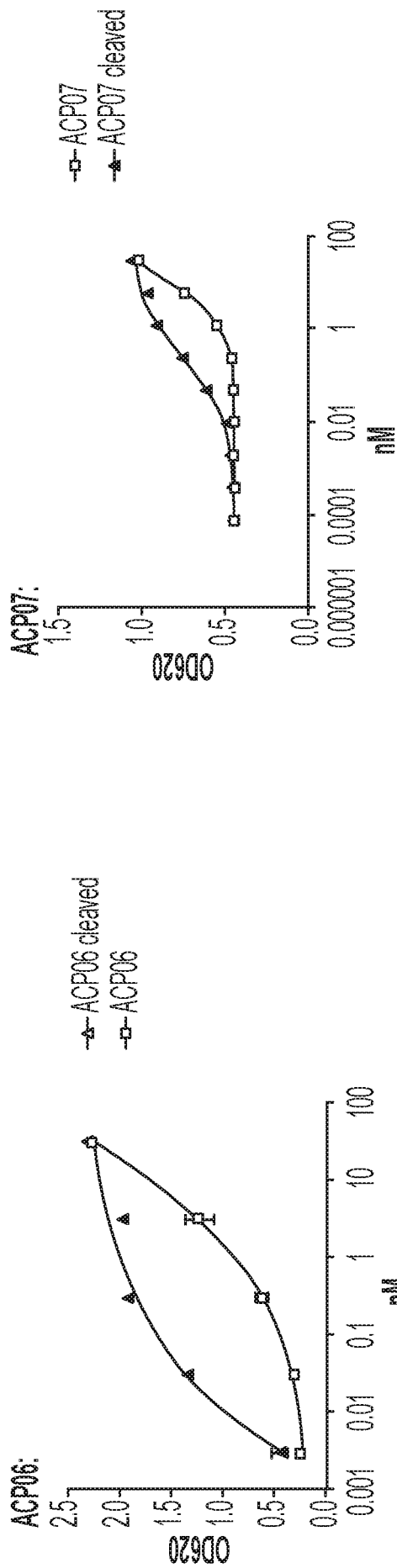


FIG. 8a

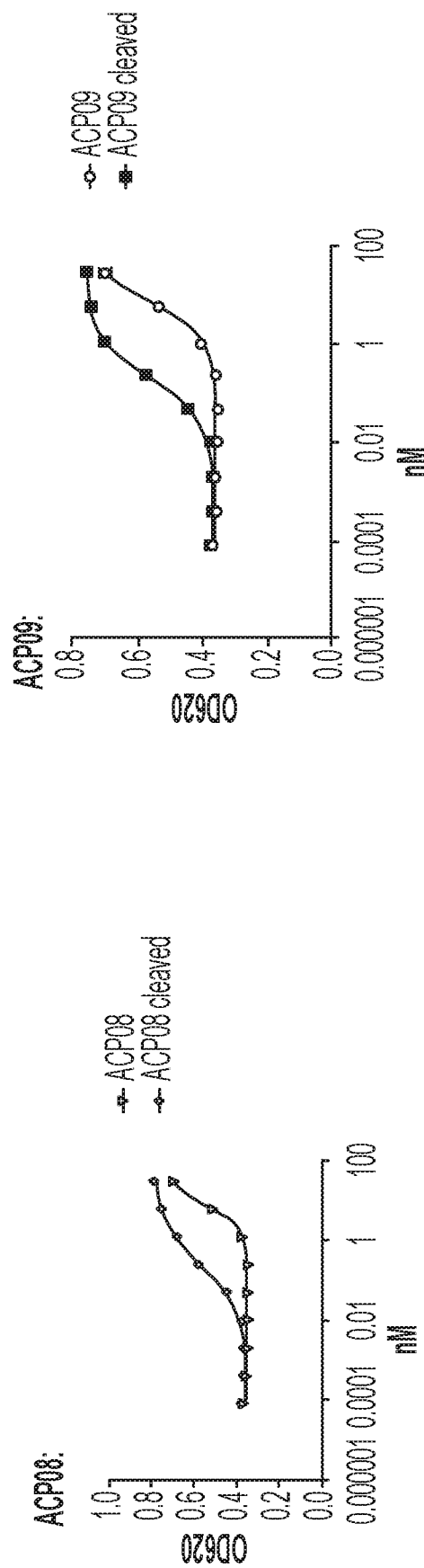


FIG. 8b

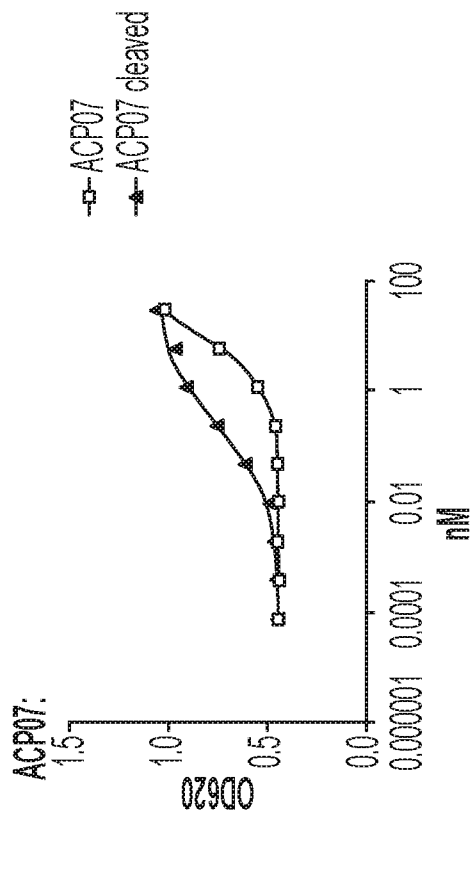


FIG. 8c

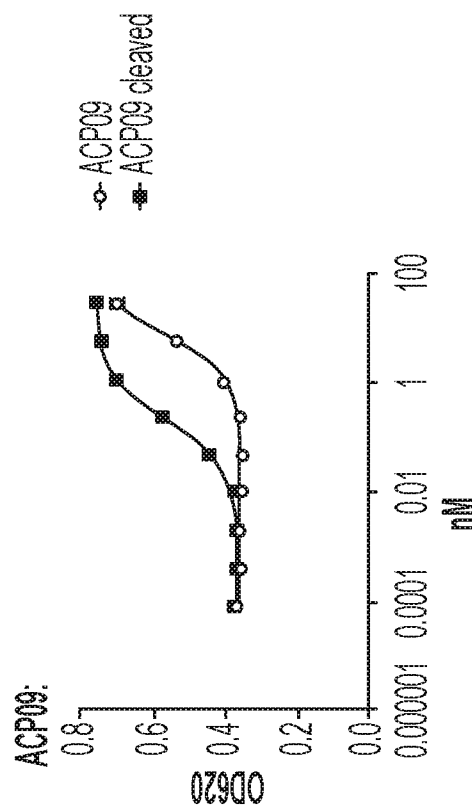


FIG. 8d

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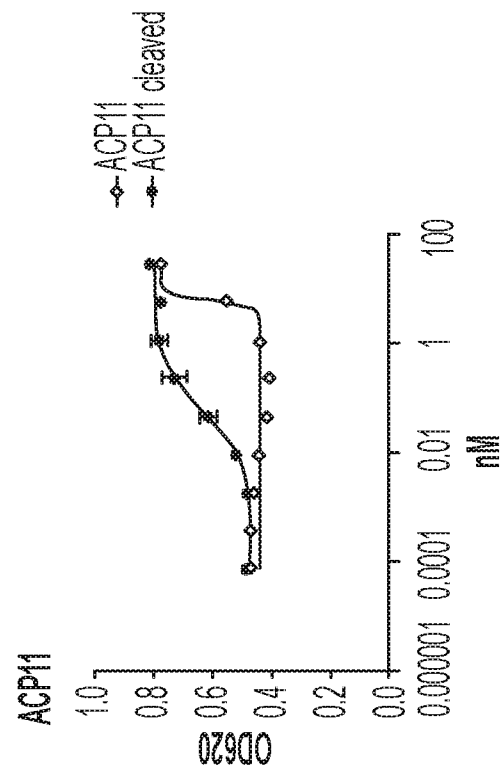


FIG. 8f

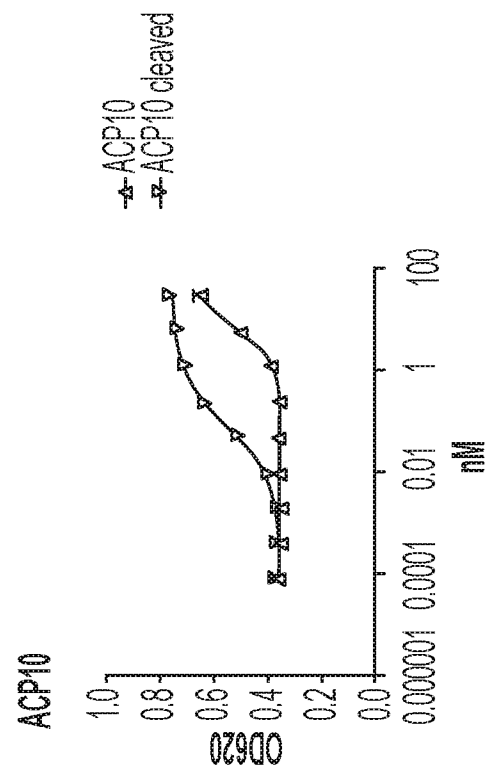


FIG. 8e

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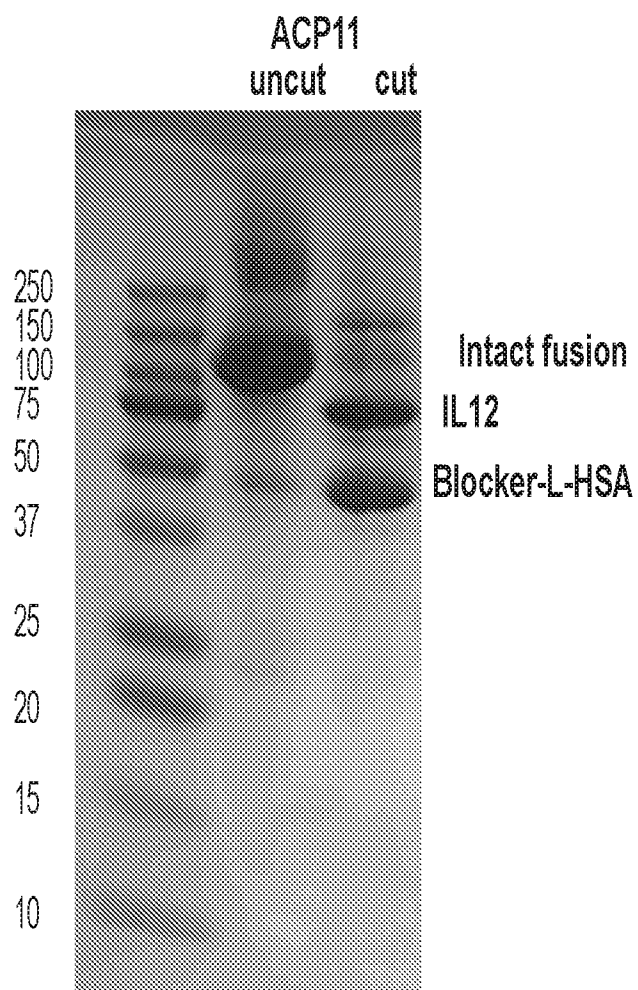


FIG. 9

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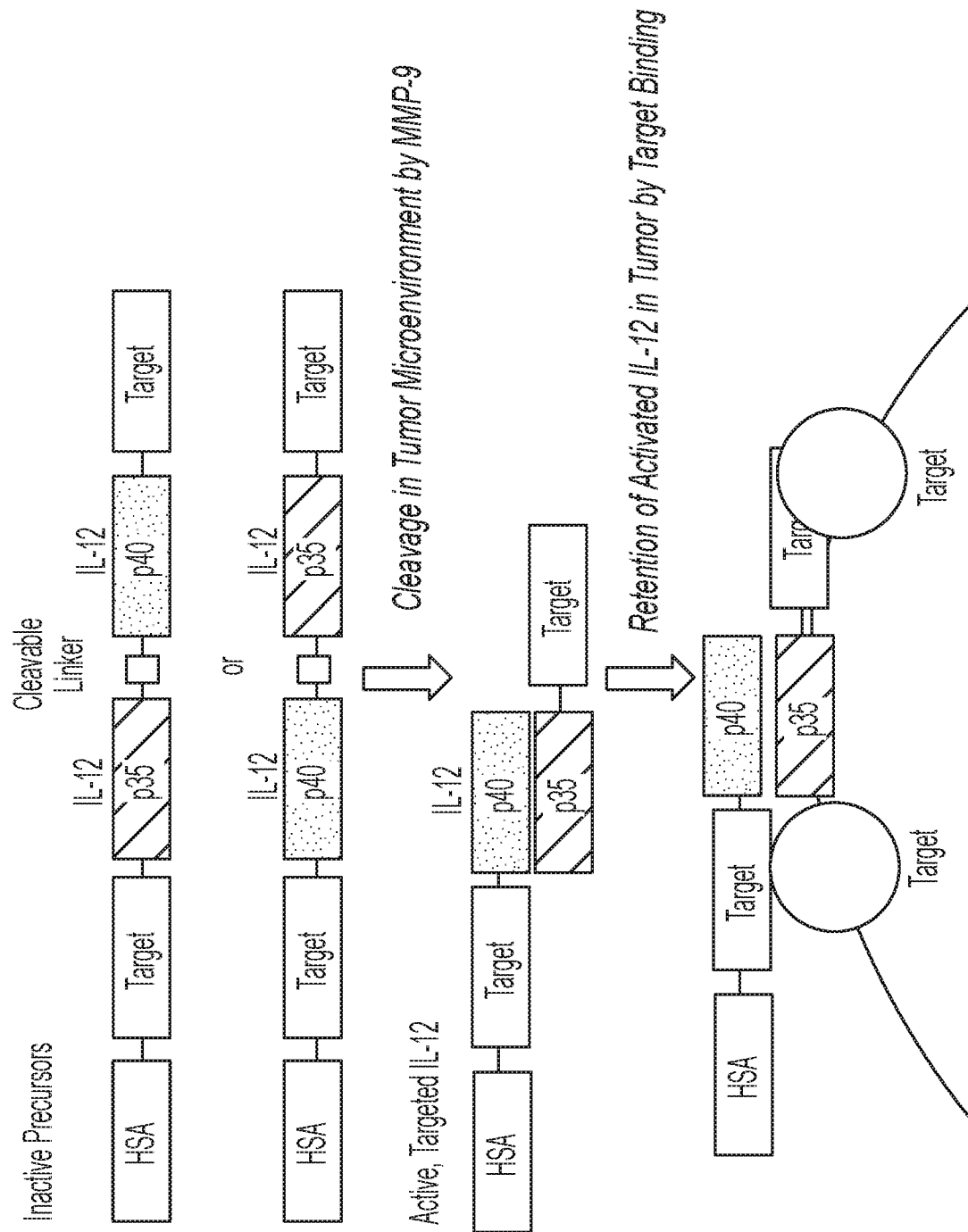


FIG. 10

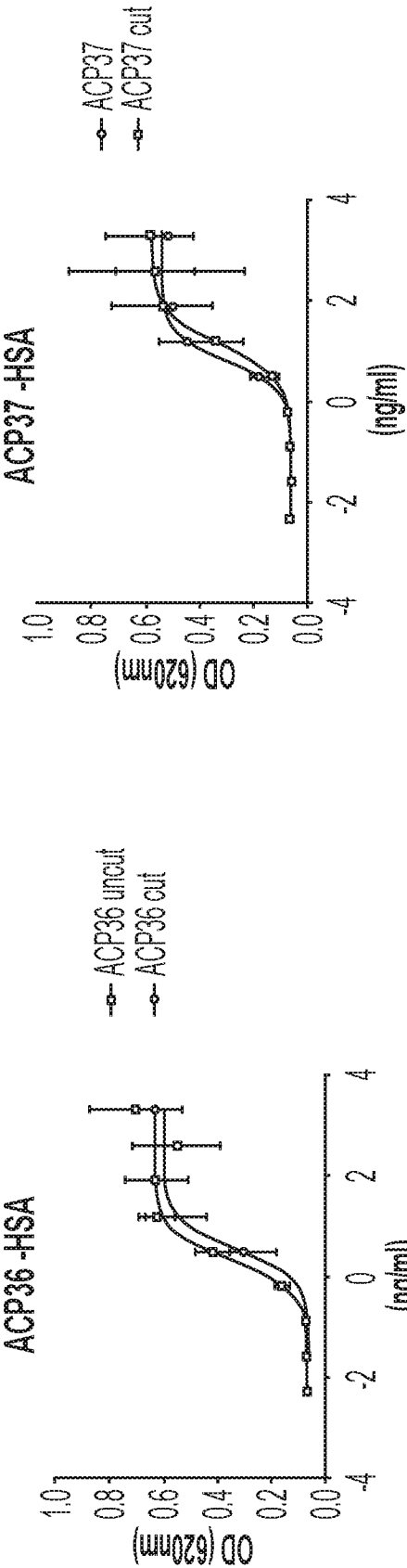


FIG. 11a

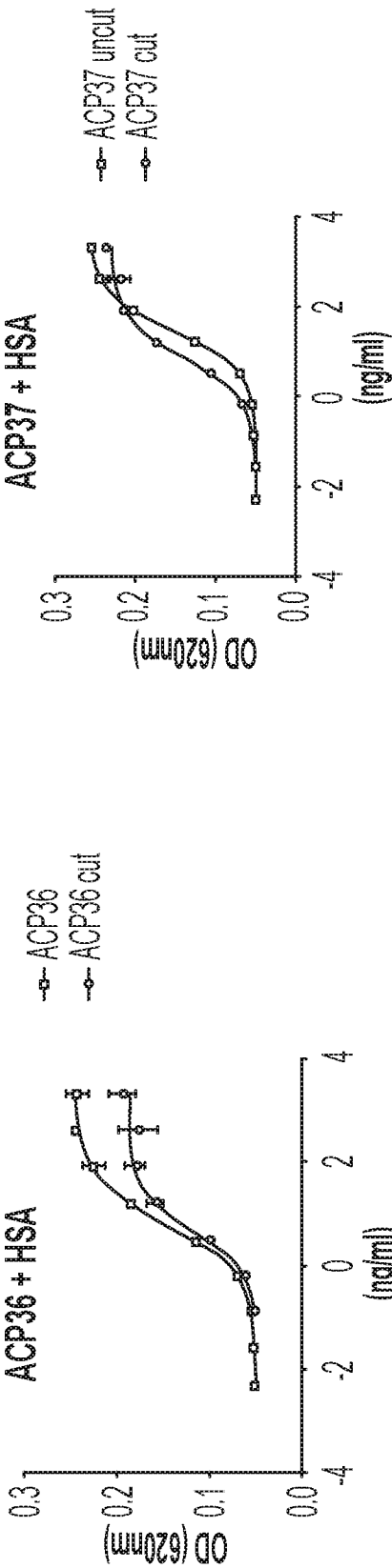


FIG. 11b

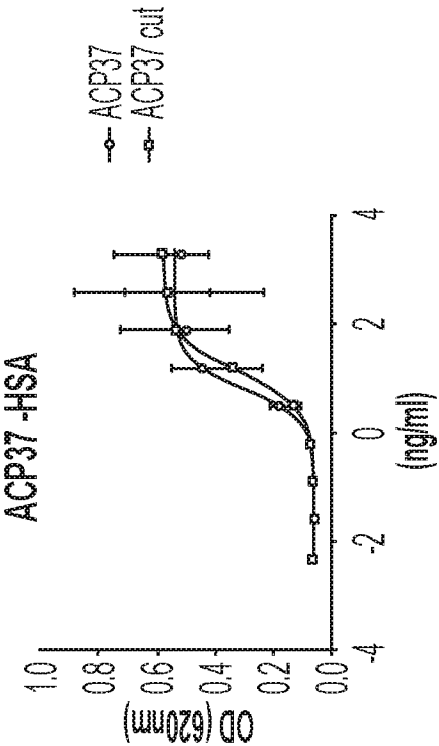


FIG. 11c

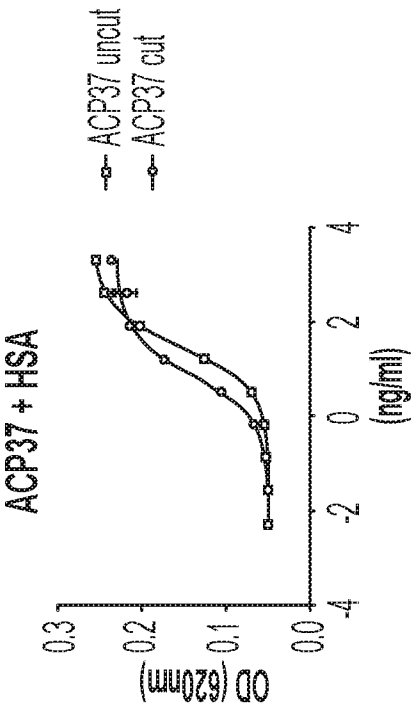


FIG. 11d

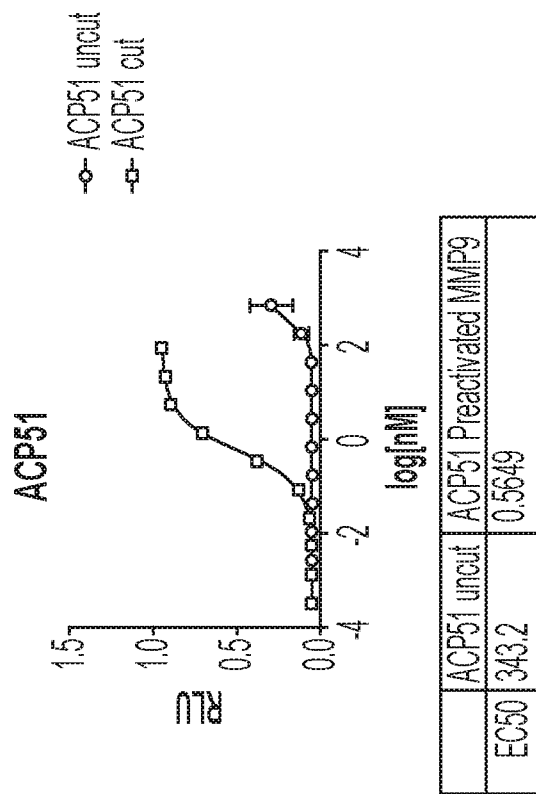
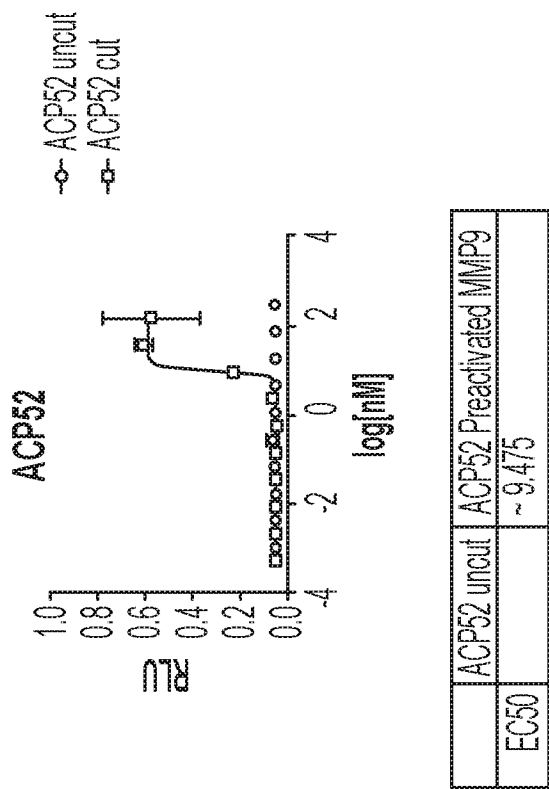


FIG. 12

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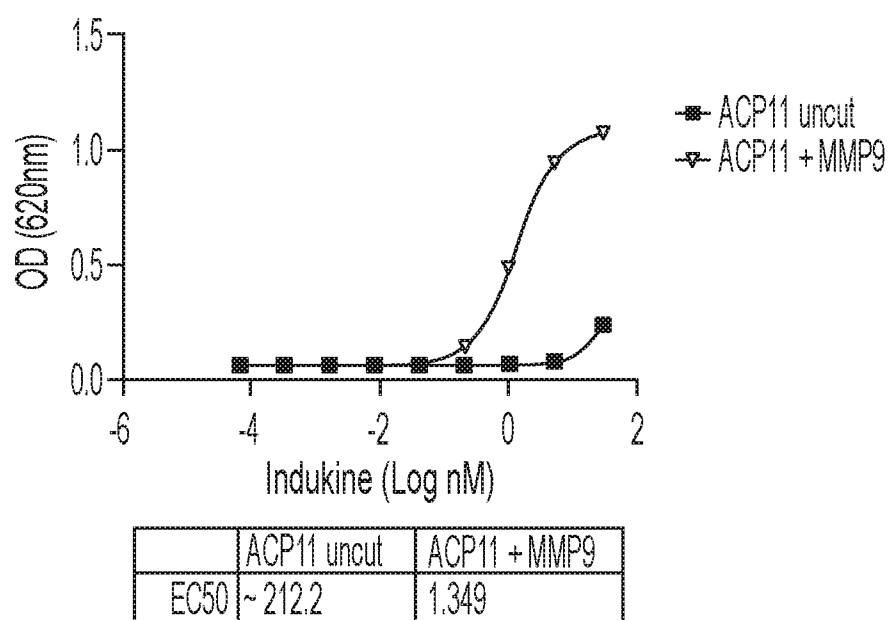


FIG. 13a

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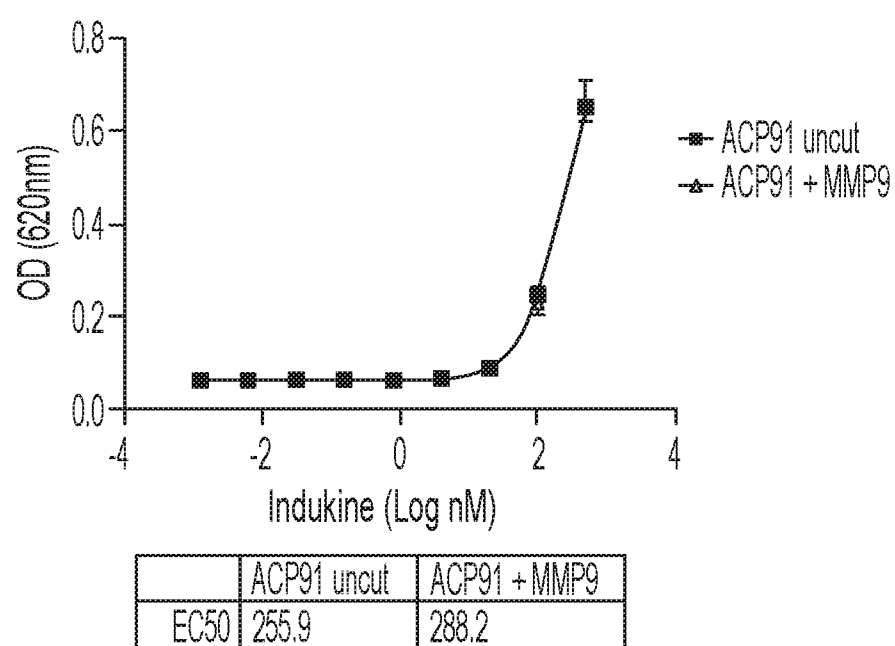


FIG. 13b

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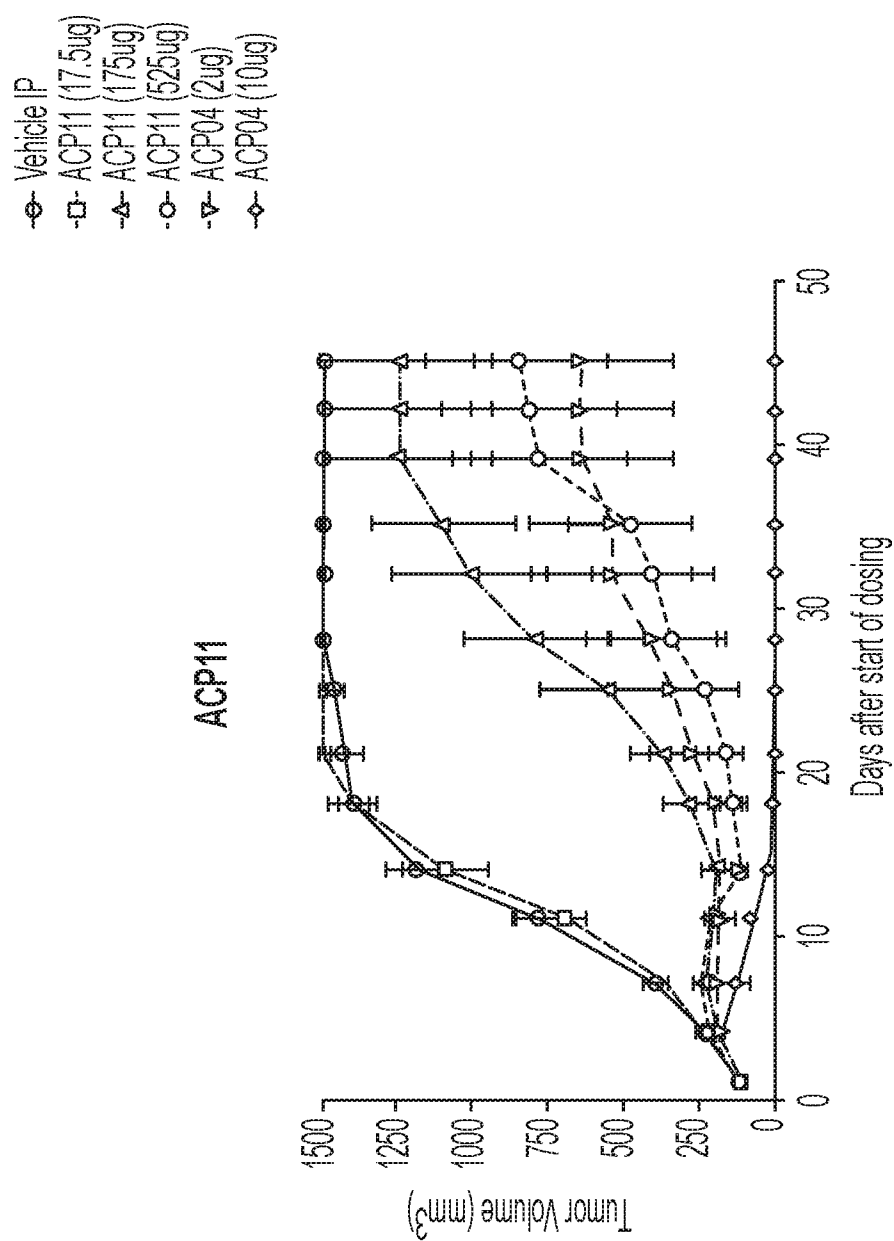


FIG. 14

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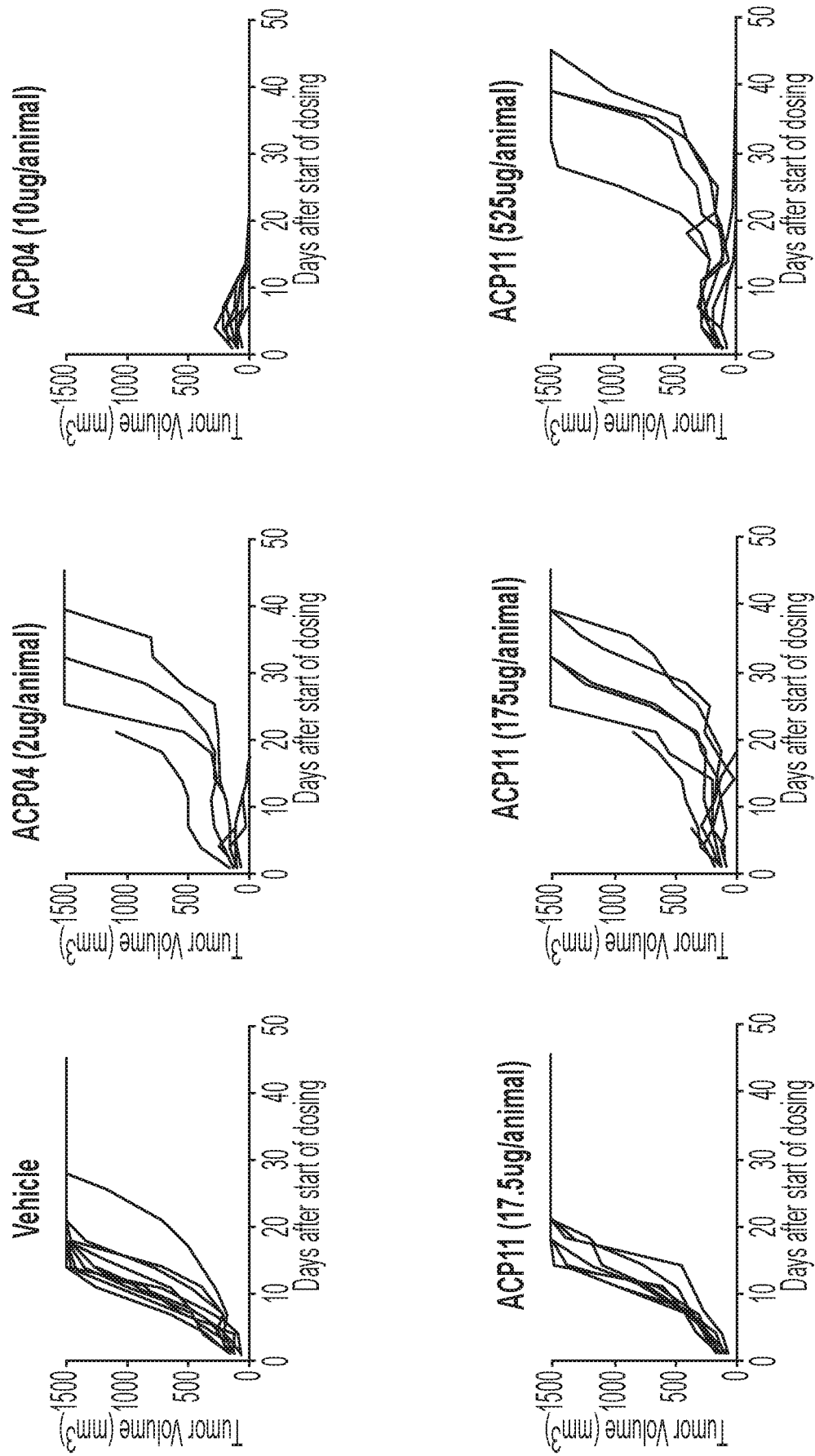
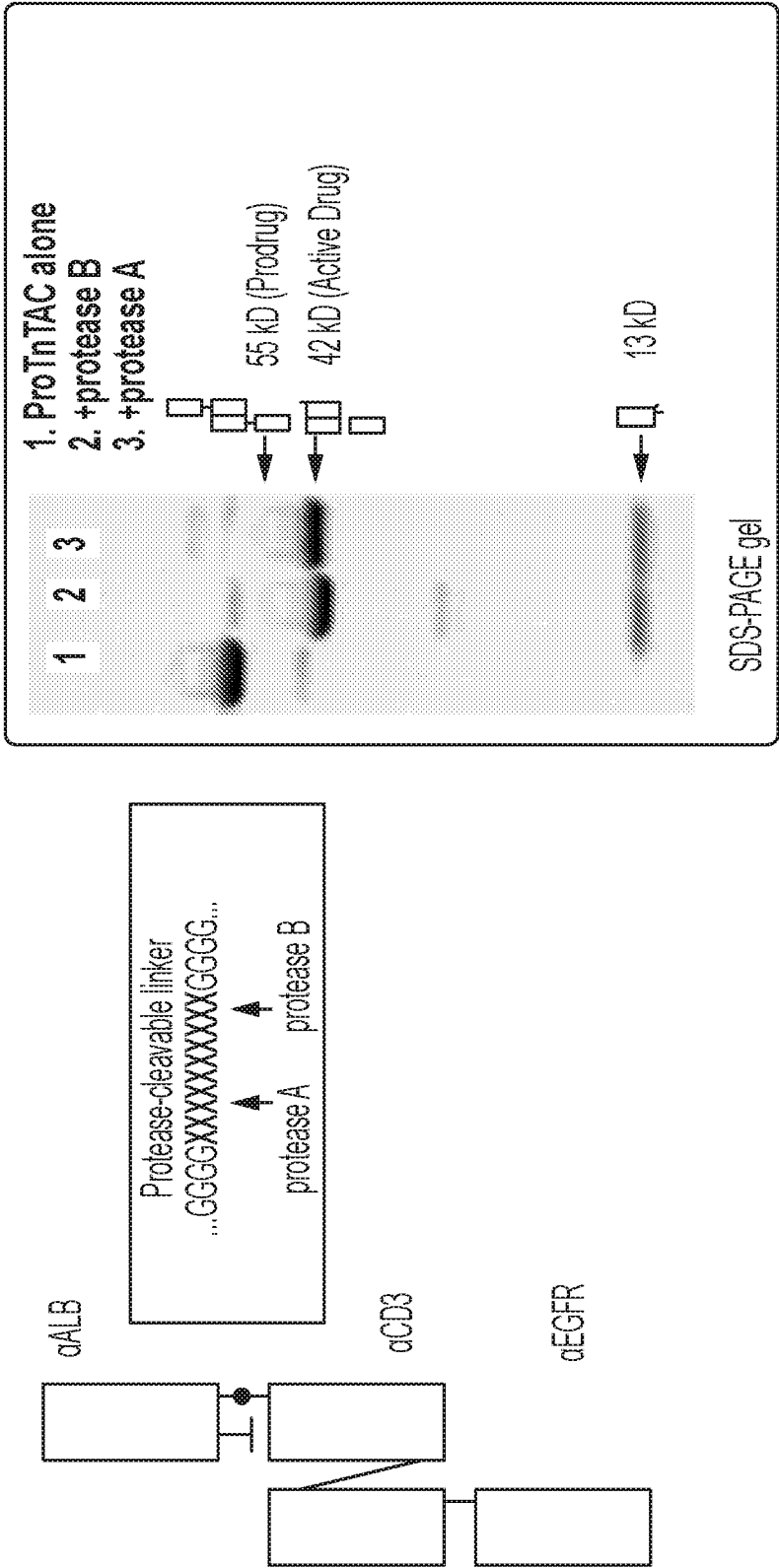


FIG. 15

ProTriTACs Are Activatable by Tumor-Associated Proteases



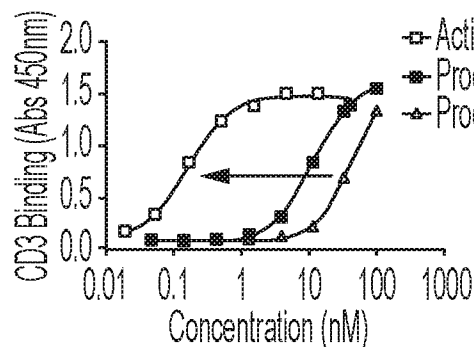
• Proprietary library of substrate linkers with different cleavability engineered

FIG. 16

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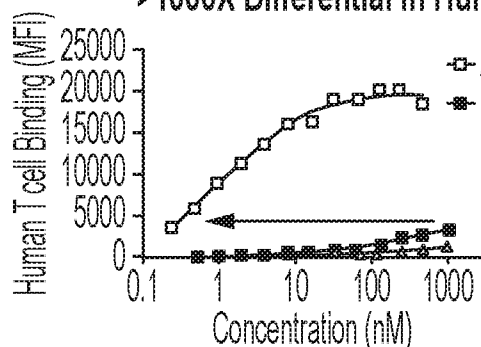
Differential Activity Supported by Various In Vitro Assays

250X Differential in CD3 Binding (ELISA)



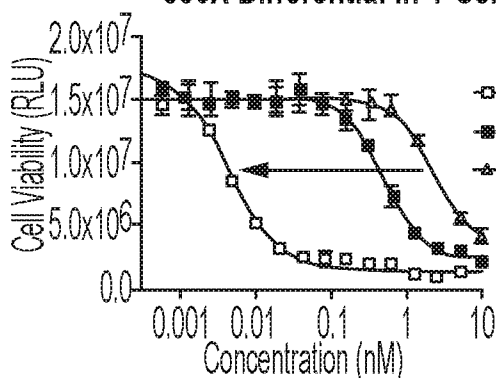
	EC50 (nM)	Masking Ratio
Active Drug	0.16	-
Prodrug	11.91	74
Prodrug (non-cleavable)	39.44	247

>1000X Differential in Human Primary T cell Binding (FACS)



	EC50 (nM)	Masking Ratio
Active Drug	1.19	-
Prodrug	>1000	n/a
Prodrug (non-cleavable)	>1000	n/a

550X Differential in T Cell Killing Activity (TDCC)



	EC50 (nM)	Masking Ratio
Active Drug	0.004	-
Prodrug	0.485	121
Prodrug (non-cleavable)	2.197	549

- Plug-and-play: masking demonstrated with >20 binders to 5 different targets

FIG. 17

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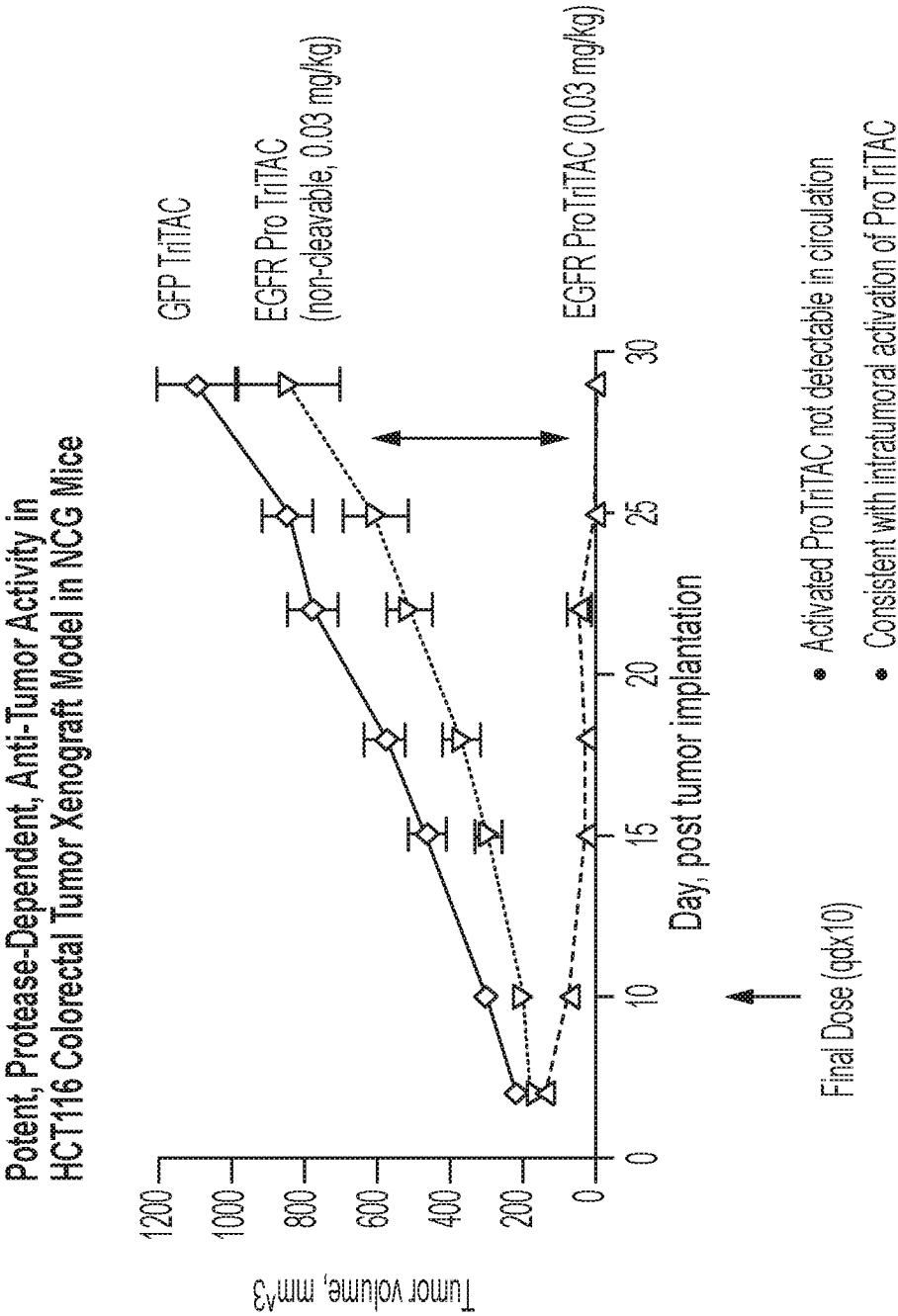


FIG. 18

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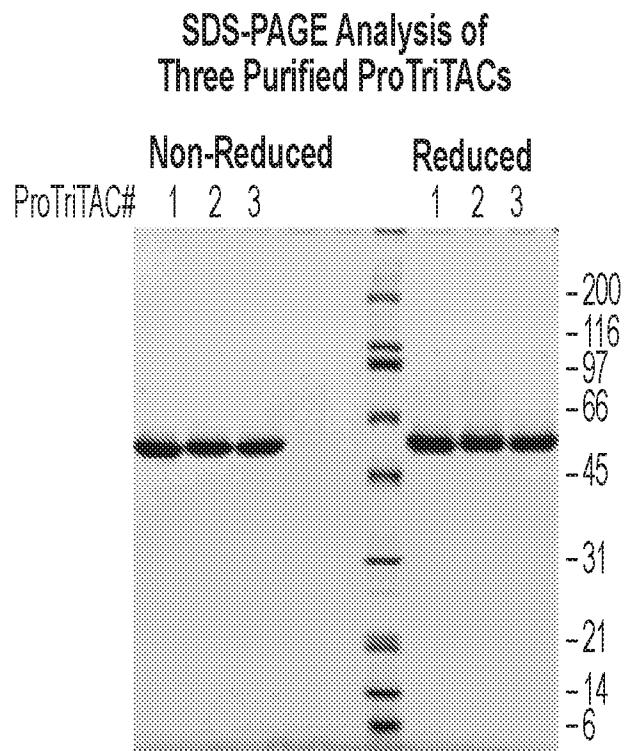
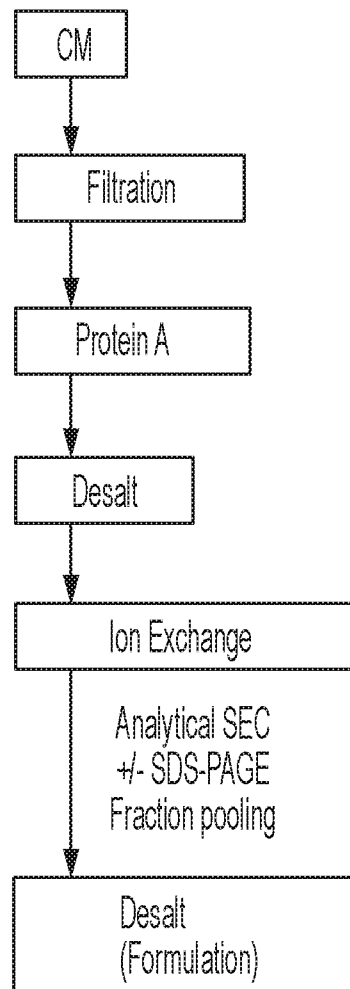
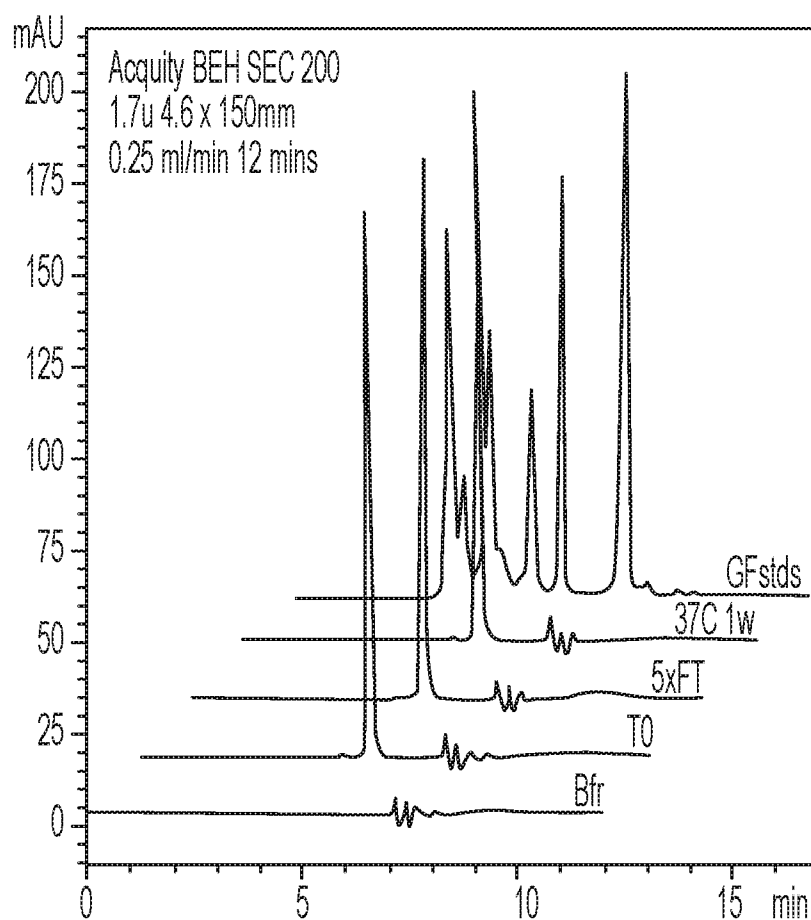


FIG. 19

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Analytical SEC of a ProTriTAC After Different Stress Conditions

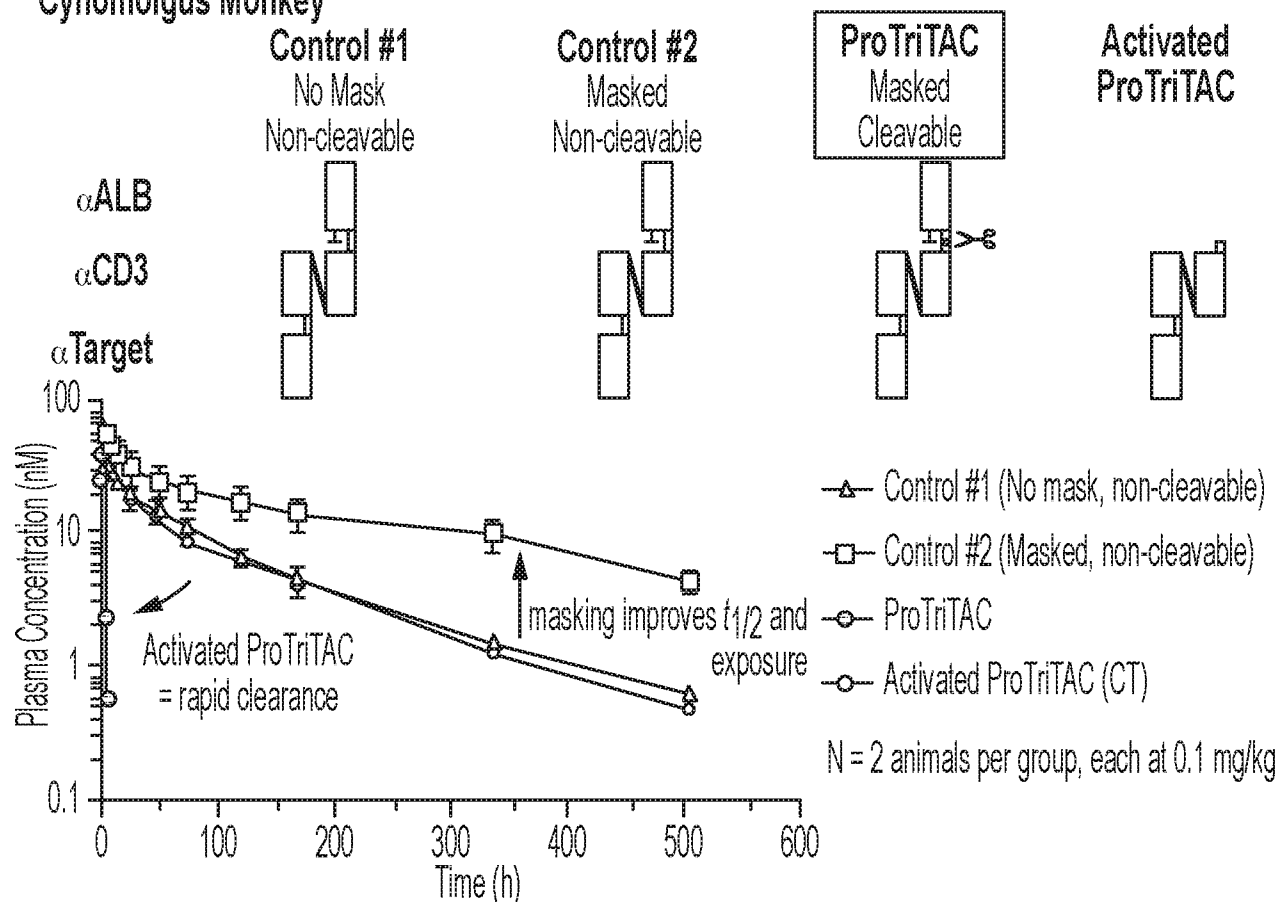


Condition	%HMW	%Main	%LMW
T0	1.7	96.0	2.3
5x FT	1.6	97.0	1.4
37C 1w	2.6	95.4	2.0

FIG. 20

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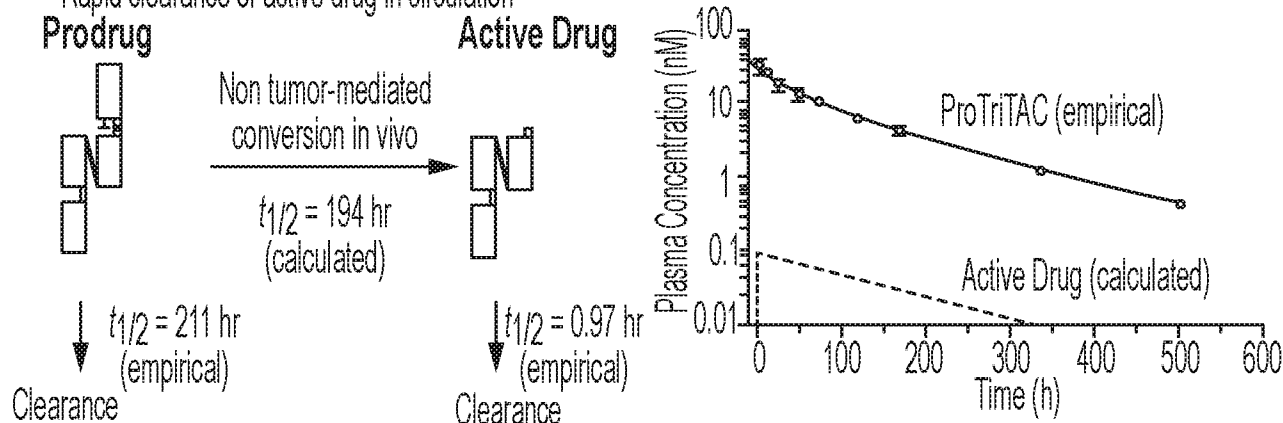
Single Dose PK Study to Investigate Functional Masking and Stability of ProTriTAC in Cynomolgus Monkey



Test Article	Terminal $t_{1/2}$ (hr)	Cmax (nM)	AUC, 0-last (hr*nM)	Clearance (mL/hr/kg)
Control #1 (No mask, non-cleavable)	118	48.2	2490	0.735
Control #2 (Masked, non-cleavable)	211	58.0	7000	0.238
ProTriTAC	101	42.7	2670	0.686
Activated ProTriTAC (CT)	0.969	66.6	41.5	58.5

Dual Protection Against On-Target, Off-Tumor Activity

- Limited peripheral T cell binding (as demonstrated by improved PK from masking)
- Rapid clearance of active drug in circulation



- Substrate linker is sufficiently stable in circulation: 50% conversion every 194 hr
- Active drug does not accumulate in circulation: below 0.5% of prodrug at all times

AMENDED SHEET

FIG. 21

SEQUENCE LISTING

<110> WEREWOLF THERAPEUTICS, INC.

<120> ACTIVATABLE INTERLEUKIN 12 POLYPEPTIDES AND METHODS OF USE THEREOF

<130> 105365-0022

<140>

<141>

<150> 62/756,515

<151> 2018-11-06

<150> 62/756,504

<151> 2018-11-06

<150> 62/671,225

<151> 2018-05-14

<160> 92

<170> PatentIn version 3.5

<210> 1

<211> 609

<212> PRT

<213> Homo sapiens

<400> 1

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

Tyr	Ser	Arg	Gly	Val	Phe	Arg	Arg	Asp	Ala	His	Lys	Ser	Glu	Val	Ala
			20					25					30		

His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu
		35				40						45			

Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Glu	Asp	His	Val
	50					55					60				

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

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

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Gly Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Cys Leu Ser Val Phe
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Gly Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly

595

600

605

Leu

<210> 2

<211> 8

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP7 cleavage domain sequence"

<400> 2

Lys Arg Ala Leu Gly Leu Pro Gly
1 5

<210> 3

<211> 40

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP7 cleavage domain sequence"

<400> 3

Asp Glu Asp Glu Asp Glu Asp Glu Asp Glu Asp Glu Asp Glu
1 5 10 15Arg Pro Leu Ala Leu Trp Arg Ser Asp Arg Asp Arg Asp Arg Asp Arg
20 25 30Asp Arg Asp Arg Asp Arg Asp Arg
35 40

<210> 4
<211> 5
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
MMP9 cleavage domain sequence"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Ile"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Thr"

<220>
<221> SITE
<222> (1)..(5)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 4
Pro Arg Ser Leu Ser
1 5

<210> 5
<211> 5
<212> PRT
<213> Unknown

<220>
<221> source

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MMP9 cleavage domain sequence"

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Leu Glu Ala Thr Ala
1 5

<210> 6

<211> 10

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP11 cleavage domain sequence"

<400> 6

Gly Gly Ala Ala Asn Leu Val Arg Gly Gly
1 5 10

<210> 7

<211> 10

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP14 cleavage domain sequence"

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Ser Gly Arg Ile Gly Phe Leu Arg Thr Ala
1 5 10

<210> 8

<211> 6

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<400> 8

Pro Leu Gly Leu Ala Gly

1 5

<210> 9

<211> 6

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<220>

<221> MOD_RES

<222> (6)..(6)

<223> Any amino acid

<400> 9

Pro Leu Gly Leu Ala Xaa

1 5

<210> 10

<211> 6

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<220>

<221> MOD_RES

<222> (4)..(4)

<223> Cys(me)

<400> 10

Pro Leu Gly Xaa Ala Gly

1 5

<210> 11

<211> 8

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<400> 11

Glu Ser Pro Ala Tyr Tyr Thr Ala

1 5

<210> 12

<211> 6

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<400> 12

Arg Leu Gln Leu Lys Leu

1 5

<210> 13

<211> 7

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
MMP cleavage domain sequence"

<400> 13
Arg Leu Gln Leu Lys Ala Cys
1 5

<210> 14
<211> 7
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
MMP2, MMP9, MMP14 cleavage domain sequence"

<220>
<221> MOD_RES
<222> (3)..(3)
<223> Cit

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Hof

<400> 14
Glu Pro Xaa Gly Xaa Tyr Leu
1 5

<210> 15
<211> 5
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Urokinase plasminogen activator (uPA) cleavage domain
sequence"

<400> 15
Ser Gly Arg Ser Ala
1 5

<210> 16
<211> 4
<212> PRT
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<220>
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Urokinase plasminogen activator (uPA) cleavage domain
sequence"

<400> 16
Asp Ala Phe Lys
1

<210> 17
<211> 5
<212> PRT
<213> Unknown

<220>
<221> source
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Urokinase plasminogen activator (uPA) cleavage domain
sequence"

<400> 17
Gly Gly Gly Arg Arg
1 5

<210> 18
<211> 4
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Lysosomal Enzyme cleavage domain sequence"

<400> 18

Gly Phe Leu Gly

1

<210> 19

<211> 4

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Lysosomal Enzyme cleavage domain sequence"

<400> 19

Ala Leu Ala Leu

1

<210> 20

<211> 2

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Lysosomal Enzyme cleavage domain sequence"

<400> 20

Phe Lys

1

<210> 21

<211> 3

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Cathepsin B cleavage domain sequence"

<400> 21

Asn Leu Leu

1

<210> 22

<211> 5

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Cathepsin D cleavage domain sequence"

<220>

<221> MOD_RES

<222> (3)..(3)

<223> Cys(Et)

<400> 22

Pro Ile Xaa Phe Phe

1

5

<210> 23

<211> 8

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Cathepsin K cleavage domain sequence"

<400> 23

Gly Gly Pro Arg Gly Leu Pro Gly

1

5

<210> 24

<211> 6

<212> PRT

<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Prostate Specific Antigen cleavage domain sequence"

<400> 24
His Ser Ser Lys Leu Gln
1 5

<210> 25
<211> 7
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Prostate Specific Antigen cleavage domain sequence"

<400> 25
His Ser Ser Lys Leu Gln Leu
1 5

<210> 26
<211> 9
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Prostate Specific Antigen cleavage domain sequence"

<400> 26
His Ser Ser Lys Leu Gln Glu Asp Ala
1 5

<210> 27
<211> 10
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Herpes Simplex Virus Protease cleavage domain sequence"

<400> 27
Leu Val Leu Ala Ser Ser Ser Phe Gly Tyr
1 5 10

<210> 28
<211> 10
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
HIV Protease cleavage domain sequence"

<400> 28
Gly Val Ser Gln Asn Tyr Pro Ile Val Gly
1 5 10

<210> 29
<211> 10
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
CMV Protease cleavage domain sequence"

<400> 29
Gly Val Val Gln Ala Ser Cys Arg Leu Ala
1 5 10

<210> 30
<211> 4
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Thrombin cleavage domain sequence"

<220>
<221> MOD_RES
<222> (2)..(2)
<223> 2-carboxy piperdine

<400> 30
Phe Xaa Arg Ser
1

<210> 31
<211> 6
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Thrombin cleavage domain sequence"

<400> 31
Asp Pro Arg Ser Phe Leu
1 5

<210> 32
<211> 6
<212> PRT
<213> Unknown

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<223> /note="Description of Unknown:
Thrombin cleavage domain sequence"

<400> 32
Pro Pro Arg Ser Phe Leu
1 5

<210> 33
<211> 4
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Caspase-3 cleavage domain sequence"

<400> 33
Asp Glu Val Asp
1

<210> 34
<211> 5
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Caspase-3 cleavage domain sequence"

<400> 34
Asp Glu Val Asp Pro
1 5

<210> 35
<211> 8
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Caspase-3 cleavage domain sequence"

<400> 35
Lys Gly Ser Gly Asp Val Glu Gly
1 5

<210> 36
<211> 6
<212> PRT
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Interleukin 1beta converting enzyme cleavage domain
sequence"

<400> 36
Gly Trp Glu His Asp Gly
1 5

<210> 37
<211> 7
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Enterokinase cleavage domain sequence"

<400> 37
Glu Asp Asp Asp Asp Lys Ala
1 5

<210> 38
<211> 9
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
FAP cleavage domain sequence"

<400> 38
Lys Gln Glu Gln Asn Pro Gly Ser Thr
1 5

<210> 39

<211> 6

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Kallikrein 2 cleavage domain sequence"

<400> 39

Gly Lys Ala Phe Arg Arg

1

5

<210> 40

<211> 4

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Plasmin cleavage domain sequence"

<400> 40

Asp Ala Phe Lys

1

<210> 41

<211> 4

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Plasmin cleavage domain sequence"

<400> 41

Asp Val Leu Lys

1

<210> 42
<211> 4
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Plasmin cleavage domain sequence"

<400> 42
Asp Ala Phe Lys
1

<210> 43
<211> 7
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
TOP cleavage domain sequence"

<400> 43
Ala Leu Leu Leu Ala Leu Leu
1 5

<210> 44
<211> 520
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 44
Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
1 5 10 15

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
20 25 30

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
35 40 45

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
50 55 60

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
65 70 75 80

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
85 90 95

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
100 105 110

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
115 120 125

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

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

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
165 170 175

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
180 185 190

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
195 200 205

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
210 215 220

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
225 230 235 240

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

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
260 265 270

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
275 280 285

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
290 295 300

Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
305 310 315 320

Ser Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser
325 330 335

Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu
340 345 350

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

Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu
370 375 380

Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr
385 390 395 400

Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr
405 410 415

Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu
420 425 430

Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile
435 440 445

Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser
450 455 460

Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu
465 470 475 480

Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala
485 490 495

Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser
500 505 510

Ser Ala His His His His His His
515 520

<210> 45

<211> 524

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 45

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
1 5 10 15

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
20 25 30

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
35 40 45

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
50 55 60

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
65 70 75 80

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
85 90 95

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
100 105 110

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
115 120 125

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

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

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
165 170 175

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
180 185 190

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
195 200 205

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
210 215 220

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
225 230 235 240

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

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
260 265 270

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
275 280 285

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
290 295 300

Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
305 310 315 320

Ser Arg Asn Leu Pro Val Ala Thr Pro Asp Pro Gly Met Phe Pro Cys
325 330 335

Leu His His Ser Gln Asn Leu Leu Arg Ala Val Ser Asn Met Leu Gln
 340 345 350

Lys Ala Arg Gln Thr Leu Glu Phe Tyr Pro Cys Thr Ser Glu Glu Ile
 355 360 365

Asp His Glu Asp Ile Thr Lys Asp Lys Thr Ser Thr Val Glu Ala Cys
 370 375 380

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

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

Phe Met Met Ala Leu Cys Leu Ser Ser Ile Tyr Glu Asp Leu Lys Met
 420 425 430

Tyr Gln Val Glu Phe Lys Thr Met Asn Ala Lys Leu Leu Met Asp Pro
 435 440 445

Lys Arg Gln Ile Phe Leu Asp Gln Asn Met Leu Ala Val Ile Asp Glu
 450 455 460

Leu Met Gln Ala Leu Asn Phe Asn Ser Glu Thr Val Pro Gln Lys Ser
 465 470 475 480

Ser Leu Glu Glu Pro Asp Phe Tyr Lys Thr Lys Ile Lys Leu Cys Ile
 485 490 495

Leu Leu His Ala Phe Arg Ile Arg Ala Val Thr Ile Asp Arg Val Met
 500 505 510

Ser Tyr Leu Asn Ala Ser His His His His His His

<210> 46

<211> 940

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46

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

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

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

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

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

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Tyr Thr
85 90 95

His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

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

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

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

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

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

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

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

His Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr Val Ser
225 230 235 240

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
245 250 255

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
260 265 270

Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser Ile Trp
275 280 285

Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr Pro Asp
290 295 300

Ala	Pro	Gly	Glu	Met	Val	Val	Leu	Thr	Cys	Asp	Thr	Pro	Glu	Glu	Asp	305	310	315	320
Gly	Ile	Thr	Trp	Thr	Leu	Asp	Gln	Ser	Ser	Glu	Val	Leu	Gly	Ser	Gly	325	330		335
Lys	Thr	Leu	Thr	Ile	Gln	Val	Lys	Glu	Phe	Gly	Asp	Ala	Gly	Gln	Tyr	340	345		350
Thr	Cys	His	Lys	Gly	Gly	Glu	Val	Leu	Ser	His	Ser	Leu	Leu	Leu	Leu	355	360		365
His	Lys	Lys	Glu	Asp	Gly	Ile	Trp	Ser	Thr	Asp	Ile	Leu	Lys	Asp	Gln	370	375		380
Lys	Glu	Pro	Lys	Asn	Lys	Thr	Phe	Leu	Arg	Cys	Glu	Ala	Lys	Asn	Tyr	385	390	395	400
Ser	Gly	Arg	Phe	Thr	Cys	Trp	Trp	Leu	Thr	Thr	Ile	Ser	Thr	Asp	Leu	405	410		415
Thr	Phe	Ser	Val	Lys	Ser	Ser	Arg	Gly	Ser	Ser	Asp	Pro	Gln	Gly	Val	420	425		430
Thr	Cys	Gly	Ala	Ala	Thr	Leu	Ser	Ala	Glu	Arg	Val	Arg	Gly	Asp	Asn	435	440		445
Lys	Glu	Tyr	Glu	Tyr	Ser	Val	Glu	Cys	Gln	Glu	Asp	Ser	Ala	Cys	Pro	450	455	460	
Ala	Ala	Glu	Glu	Ser	Leu	Pro	Ile	Glu	Val	Met	Val	Asp	Ala	Val	His	465	470	475	480
Lys	Leu	Lys	Tyr	Glu	Asn	Tyr	Thr	Ser	Ser	Phe	Phe	Ile	Arg	Asp	Ile				

485

490

495

Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu Lys Asn
500 505 510

Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp Ser Thr
515 520 525

Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln Gly Lys
530 535 540

Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr Ser Ala
545 550 555 560

Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala Gln Asp
565 570 575

Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro Cys Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Arg
595 600 605

Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser Arg Asn
610 615 620

Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu Lys Leu
625 630 635 640

Lys His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp Ile Thr
645 650 655

Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu Leu His
660 665 670

Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr Thr Arg
675 680 685

Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr Leu Cys
690 695 700

Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu Phe Gln
705 710 715 720

Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile Ile Leu
725 730 735

Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser Leu Asn
740 745 750

His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu Ala Asp
755 760 765

Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe Ser
770 775 780

Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser Ala
785 790 795 800

Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser Glu
805 810 815

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn Ser
820 825 830

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe Gly
835 840 845

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
850 855 860

Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val Lys
865 870 875 880

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr Leu
885 890 895

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr
900 905 910

Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr Val
915 920 925

Ser Ser His His His His His His Glu Pro Glu Ala
930 935 940

<210> 47

<211> 1069

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47

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

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

Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu

35

40

45

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

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

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Tyr Thr
85 90 95

His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

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

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

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

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

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

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

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

His Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr Val Ser
225 230 235 240

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
245 250 255

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
260 265 270

Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser Ile Trp
275 280 285

Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr Pro Asp
290 295 300

Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu Glu Asp
305 310 315 320

Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly Ser Gly
325 330 335

Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly Gln Tyr
340 345 350

Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu Leu Leu
355 360 365

His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys Asp Gln
370 375 380

Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys Asn Tyr
385 390 395 400

Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr Asp Leu
405 410 415

Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln Gly Val
420 425 430

Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly Asp Asn
435 440 445

Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala Cys Pro
450 455 460

Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala Val His
465 470 475 480

Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg Asp Ile
485 490 495

Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu Lys Asn
500 505 510

Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp Ser Thr
515 520 525

Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln Gly Lys
530 535 540

Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr Ser Ala
545 550 555 560

Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala Gln Asp
565 570 575

Arg	Tyr	Tyr	Ser	Ser	Ser	Trp	Ser	Glu	Trp	Ala	Ser	Val	Pro	Cys	Ser			
			580					585					590					
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg			
			595				600					605						
Val	Ile	Pro	Val	Ser	Gly	Pro	Ala	Arg	Cys	Leu	Ser	Gln	Ser	Arg	Asn			
	610					615					620							
Leu	Leu	Lys	Thr	Thr	Asp	Asp	Met	Val	Lys	Thr	Ala	Arg	Glu	Lys	Leu			
625					630					635					640			
Lys	His	Tyr	Ser	Cys	Thr	Ala	Glu	Asp	Ile	Asp	His	Glu	Asp	Ile	Thr			
				645					650					655				
Arg	Asp	Gln	Thr	Ser	Thr	Leu	Lys	Thr	Cys	Leu	Pro	Leu	Glu	Leu	His			
			660					665					670					
Lys	Asn	Glu	Ser	Cys	Leu	Ala	Thr	Arg	Glu	Thr	Ser	Ser	Thr	Thr	Arg			
		675					680					685						
Gly	Ser	Cys	Leu	Pro	Pro	Gln	Lys	Thr	Ser	Leu	Met	Met	Thr	Leu	Cys			
	690					695					700							
Leu	Gly	Ser	Ile	Tyr	Glu	Asp	Leu	Lys	Met	Tyr	Gln	Thr	Glu	Phe	Gln			
705					710					715					720			
Ala	Ile	Asn	Ala	Ala	Leu	Gln	Asn	His	Asn	His	Gln	Gln	Ile	Ile	Leu			
				725					730					735				
Asp	Lys	Gly	Met	Leu	Val	Ala	Ile	Asp	Glu	Leu	Met	Gln	Ser	Leu	Asn			
			740					745					750					
His	Asn	Gly	Glu	Thr	Leu	Arg	Gln	Lys	Pro	Pro	Val	Gly	Glu	Ala	Asp			

755

760

765

Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe Ser
 770 775 780

Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser Ala
 785 790 795 800

Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser Glu
 805 810 815

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn Ser
 820 825 830

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe Gly
 835 840 845

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
 850 855 860

Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val Lys
 865 870 875 880

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr Leu
 885 890 895

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr
 900 905 910

Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr Val
 915 920 925

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 930 935 940

Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly
945 950 955 960

Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Asn
965 970 975

Ser Val Met Ala Trp Tyr Arg Gln Thr Pro Gly Lys Gln Arg Glu Phe
980 985 990

Val Ala Ile Ile Asn Ser Val Gly Ser Thr Asn Tyr Ala Asp Ser Val
995 1000 1005

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
1010 1015 1020

Tyr Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr
1025 1030 1035

Val Cys Asn Arg Asn Phe Asp Arg Ile Tyr Trp Gly Gln Gly Thr
1040 1045 1050

Gln Val Thr Val Ser Ser His His His His His His Glu Pro Glu
1055 1060 1065

Ala

<210> 48

<211> 1069

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48

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

Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Asn Ser
20 25 30

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

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

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

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

Arg Asn Phe Asp Arg Ile Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
100 105 110

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

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

Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg Ser Asn Ile Gly Ser
145 150 155 160

Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu

165

170

175

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

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
195 200 205

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Tyr
210 215 220

Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu
225 230 235 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
245 250 255

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

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly
275 280 285

Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
290 295 300

Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
305 310 315 320

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
325 330 335

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

Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr Val
355 360 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
370 375 380

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
385 390 395 400

Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser Ile
405 410 415

Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr Pro
420 425 430

Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu Glu
435 440 445

Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly Ser
450 455 460

Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly Gln
465 470 475 480

Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu Leu
485 490 495

Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys Asp
500 505 510

Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys Asn
515 520 525

Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr Asp
530 535 540

Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln Gly
545 550 555 560

Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly Asp
565 570 575

Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala Cys
580 585 590

Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala Val
595 600 605

His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg Asp
610 615 620

Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu Lys
625 630 635 640

Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp Ser
645 650 655

Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln Gly
660 665 670

Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr Ser
675 680 685

Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala Gln
690 695 700

Asp	Arg	Tyr	Tyr	Ser	Ser	Ser	Trp	Ser	Glu	Trp	Ala	Ser	Val	Pro	Cys
705					710					715					720
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
				725					730						735
Arg	Val	Ile	Pro	Val	Ser	Gly	Pro	Ala	Arg	Cys	Leu	Ser	Gln	Ser	Arg
			740					745					750		
Asn	Leu	Leu	Lys	Thr	Thr	Asp	Asp	Met	Val	Lys	Thr	Ala	Arg	Glu	Lys
		755					760					765			
Leu	Lys	His	Tyr	Ser	Cys	Thr	Ala	Glu	Asp	Ile	Asp	His	Glu	Asp	Ile
	770					775					780				
Thr	Arg	Asp	Gln	Thr	Ser	Thr	Leu	Lys	Thr	Cys	Leu	Pro	Leu	Glu	Leu
785					790					795					800
His	Lys	Asn	Glu	Ser	Cys	Leu	Ala	Thr	Arg	Glu	Thr	Ser	Ser	Thr	Thr
				805					810					815	
Arg	Gly	Ser	Cys	Leu	Pro	Pro	Gln	Lys	Thr	Ser	Leu	Met	Met	Thr	Leu
			820					825					830		
Cys	Leu	Gly	Ser	Ile	Tyr	Glu	Asp	Leu	Lys	Met	Tyr	Gln	Thr	Glu	Phe
		835					840					845			
Gln	Ala	Ile	Asn	Ala	Ala	Leu	Gln	Asn	His	Asn	His	Gln	Gln	Ile	Ile
	850					855					860				
Leu	Asp	Lys	Gly	Met	Leu	Val	Ala	Ile	Asp	Glu	Leu	Met	Gln	Ser	Leu
865					870					875					880
Asn	His	Asn	Gly	Glu	Thr	Leu	Arg	Gln	Lys	Pro	Pro	Val	Gly	Glu	Ala

885

890

895

Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe
900 905 910

Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser
915 920 925

Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser
930 935 940

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
945 950 955 960

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
965 970 975

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
980 985 990

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val
995 1000 1005

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu
1010 1015 1020

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr
1025 1030 1035

Tyr Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr
1040 1045 1050

Leu Val Thr Val Ser Ser His His His His His His Glu Pro Glu
1055 1060 1065

Ala

<210> 49

<211> 940

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 49

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

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

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

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

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly		
		115					120					125					
Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Gly	Ala	Pro		
		130				135					140						
Gly	Gln	Arg	Val	Thr	Ile	Ser	Cys	Ser	Gly	Ser	Arg	Ser	Asn	Ile	Gly		
145					150					155					160		
Ser	Asn	Thr	Val	Lys	Trp	Tyr	Gln	Gln	Leu	Pro	Gly	Thr	Ala	Pro	Lys		
				165					170					175			
Leu	Leu	Ile	Tyr	Tyr	Asn	Asp	Gln	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg		
			180					185					190				
Phe	Ser	Gly	Ser	Lys	Ser	Gly	Thr	Ser	Ala	Ser	Leu	Ala	Ile	Thr	Gly		
		195					200					205					
Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Arg		
	210					215					220						
Tyr	Thr	His	Pro	Ala	Leu	Leu	Phe	Gly	Thr	Gly	Thr	Lys	Val	Thr	Val		
225					230					235					240		
Leu	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser		
				245					250					255			
Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg		
			260					265					270				
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr		
		275					280					285					
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		

290

295

300

Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 305 310 315 320

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 325 330 335

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 340 345 350

Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr
 355 360 365

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 385 390 395 400

Ser Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser
 405 410 415

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
 420 425 430

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
 435 440 445

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
 450 455 460

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
 465 470 475 480

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
485 490 495

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
500 505 510

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
515 520 525

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr
530 535 540

Asp Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp Pro Gln
545 550 555 560

Gly Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val Arg Gly
565 570 575

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
580 585 590

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
595 600 605

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
610 615 620

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
625 630 635 640

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
645 650 655

Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln Val Gln
660 665 670

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
675 680 685

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
690 695 700

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
705 710 715 720

Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
725 730 735

Ser Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser
740 745 750

Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu
755 760 765

Lys Leu Lys His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp
770 775 780

Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu
785 790 795 800

Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr
805 810 815

Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr
820 825 830

Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu
835 840 845

Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile
850 855 860

Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser
865 870 875 880

Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu
885 890 895

Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala
900 905 910

Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser
915 920 925

Ser Ala His His His His His His Glu Pro Glu Ala
930 935 940

<210> 50

<211> 940

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"
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<400> 50

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

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

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

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

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro
115 120 125

Gly Ser Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp
130 135 140

Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr
145 150 155 160

Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val
165 170 175

Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp
180 185 190

Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser
195 200 205

Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile
210 215 220

Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu
225 230 235 240

Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile
245 250 255

Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg Gly Ser Ser Asp
260 265 270

Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser Ala Glu Arg Val
275 280 285

Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp
290 295 300

Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val
305 310 315 320

Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe
325 330 335

Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys
340 345 350

Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp
355 360 365

Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr Phe Cys Val Gln
370 375 380

Val	Gln	Gly	Lys	Ser	Lys	Arg	Glu	Lys	Lys	Asp	Arg	Val	Phe	Thr	Asp	385	390	395	400
Lys	Thr	Ser	Ala	Thr	Val	Ile	Cys	Arg	Lys	Asn	Ala	Ser	Ile	Ser	Val	405	410	415	
Arg	Ala	Gln	Asp	Arg	Tyr	Tyr	Ser	Ser	Ser	Trp	Ser	Glu	Trp	Ala	Ser	420	425	430	
Val	Pro	Cys	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	435	440	445	
Gly	Gly	Ser	Arg	Val	Ile	Pro	Val	Ser	Gly	Pro	Ala	Arg	Cys	Leu	Ser	450	455	460	
Gln	Ser	Arg	Asn	Leu	Leu	Lys	Thr	Thr	Asp	Asp	Met	Val	Lys	Thr	Ala	465	470	475	480
Arg	Glu	Lys	Leu	Lys	His	Tyr	Ser	Cys	Thr	Ala	Glu	Asp	Ile	Asp	His	485	490	495	
Glu	Asp	Ile	Thr	Arg	Asp	Gln	Thr	Ser	Thr	Leu	Lys	Thr	Cys	Leu	Pro	500	505	510	
Leu	Glu	Leu	His	Lys	Asn	Glu	Ser	Cys	Leu	Ala	Thr	Arg	Glu	Thr	Ser	515	520	525	
Ser	Thr	Thr	Arg	Gly	Ser	Cys	Leu	Pro	Pro	Gln	Lys	Thr	Ser	Leu	Met	530	535	540	
Met	Thr	Leu	Cys	Leu	Gly	Ser	Ile	Tyr	Glu	Asp	Leu	Lys	Met	Tyr	Gln	545	550	555	560
Thr	Glu	Phe	Gln	Ala	Ile	Asn	Ala	Ala	Leu	Gln	Asn	His	Asn	His	Gln				

565

570

575

Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met
580 585 590

Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val
595 600 605

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

His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr
625 630 635 640

Leu Ser Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu
645 650 655

Pro Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
660 665 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
675 680 685

Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly
690 695 700

Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg Ser Asn Ile Gly Ser
705 710 715 720

Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
725 730 735

Leu Ile Tyr Tyr Asn Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
740 745 750

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
755 760 765

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Tyr
770 775 780

Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu
785 790 795 800

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
805 810 815

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
820 825 830

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly
835 840 845

Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
850 855 860

Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
865 870 875 880

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
885 890 895

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Lys
900 905 910

Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr Val
915 920 925

Ser Ser His His His His His His Glu Pro Glu Ala
930 935 940

<210> 51

<211> 940

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 51

Ile Trp Glu Leu Lys Lys Asp Val Tyr Val Val Glu Leu Asp Trp Tyr
1 5 10 15

Pro Asp Ala Pro Gly Glu Met Val Val Leu Thr Cys Asp Thr Pro Glu
20 25 30

Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln Ser Ser Glu Val Leu Gly
35 40 45

Ser Gly Lys Thr Leu Thr Ile Gln Val Lys Glu Phe Gly Asp Ala Gly
50 55 60

Gln Tyr Thr Cys His Lys Gly Gly Glu Val Leu Ser His Ser Leu Leu
65 70 75 80

Leu Leu His Lys Lys Glu Asp Gly Ile Trp Ser Thr Asp Ile Leu Lys
85 90 95

Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe Leu Arg Cys Glu Ala Lys
100 105 110

Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp Leu Thr Thr Ile Ser Thr

115

120

125

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

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

Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu Cys Gln Glu Asp Ser Ala
 165 170 175

Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile Glu Val Met Val Asp Ala
 180 185 190

Val His Lys Leu Lys Tyr Glu Asn Tyr Thr Ser Ser Phe Phe Ile Arg
 195 200 205

Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Leu Lys Pro Leu
 210 215 220

Lys Asn Ser Arg Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Thr Trp
 225 230 235 240

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

Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg Val Phe Thr Asp Lys Thr
 260 265 270

Ser Ala Thr Val Ile Cys Arg Lys Asn Ala Ser Ile Ser Val Arg Ala
 275 280 285

Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser Glu Trp Ala Ser Val Pro
 290 295 300

Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
305 310 315 320

Ser Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser
325 330 335

Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu
340 345 350

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

Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu
370 375 380

Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr
385 390 395 400

Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr
405 410 415

Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu
420 425 430

Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile
435 440 445

Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser
450 455 460

Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu
465 470 475 480

Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala
485 490 495

Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser
500 505 510

Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly
515 520 525

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
530 535 540

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
545 550 555 560

Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln Arg
565 570 575

Val Thr Ile Ser Cys Ser Gly Ser Arg Ser Asn Ile Gly Ser Asn Thr
580 585 590

Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile
595 600 605

Tyr Tyr Asn Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly
610 615 620

Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala
625 630 635 640

Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Tyr Thr His
645 650 655

Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gly
660 665 670

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
675 680 685

Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg
690 695 700

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His
705 710 715 720

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Phe Ile
725 730 735

Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly Arg
740 745 750

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
755 760 765

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Lys Thr His
770 775 780

Gly Ser His Asp Asn Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
785 790 795 800

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
805 810 815

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn Ser
820 825 830

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe Gly

835

840

845

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
 850 855 860

Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val Lys
 865 870 875 880

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr Leu
 885 890 895

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr
 900 905 910

Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr Val
 915 920 925

Ser Ser His His His His His His Glu Pro Glu Ala
 930 935 940

<210> 52

<211> 328

<212> PRT

<213> Homo sapiens

<400> 52

Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
 1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
 20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
 35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

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

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn

225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser
325

<210> 53

<211> 215

<212> PRT

<213> Mus musculus

<400> 53

Met Cys Gln Ser Arg Tyr Leu Leu Phe Leu Ala Thr Leu Ala Leu Leu
1 5 10 15

Asn His Leu Ser Leu Ala Arg Val Ile Pro Val Ser Gly Pro Ala Arg
20 25 30

Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val
35 40 45

Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu Asp
50 55 60

Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr
65 70 75 80

Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg
85 90 95

Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr
100 105 110

Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys
115 120 125

Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His
130 135 140

Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp
145 150 155 160

Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys
165 170 175

Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys
180 185 190

Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val
195 200 205

Met Gly Tyr Leu Ser Ser Ala
210 215

<210> 54

<211> 862
<212> PRT
<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
IL12Rb-2 sequence"

<400> 54

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

Thr Trp Leu Leu Ile Lys Ala Lys Ile Asp Ala Cys Lys Arg Gly Asp
20 25 30

Val Thr Val Lys Pro Ser His Val Ile Leu Leu Gly Ser Thr Val Asn
35 40 45

Ile Thr Cys Ser Leu Lys Pro Arg Gln Gly Cys Phe His Tyr Ser Arg
50 55 60

Arg Asn Lys Leu Ile Leu Tyr Lys Phe Asp Arg Arg Ile Asn Phe His
65 70 75 80

His Gly His Ser Leu Asn Ser Gln Val Thr Gly Leu Pro Leu Gly Thr
85 90 95

Thr Leu Phe Val Cys Lys Leu Ala Cys Ile Asn Ser Asp Glu Ile Gln
100 105 110

Ile Cys Gly Ala Glu Ile Phe Val Gly Val Ala Pro Glu Gln Pro Gln
115 120 125

Asn Leu Ser Cys Ile Gln Lys Gly Glu Gln Gly Thr Val Ala Cys Thr
130 135 140

Trp Glu Arg Gly Arg Asp Thr His Leu Tyr Thr Glu Tyr Thr Leu Gln
145 150 155 160

Leu Ser Gly Pro Lys Asn Leu Thr Trp Gln Lys Gln Cys Lys Asp Ile
165 170 175

Tyr Cys Asp Tyr Leu Asp Phe Gly Ile Asn Leu Thr Pro Glu Ser Pro
180 185 190

Glu Ser Asn Phe Thr Ala Lys Val Thr Ala Val Asn Ser Leu Gly Ser
195 200 205

Ser Ser Ser Leu Pro Ser Thr Phe Thr Phe Leu Asp Ile Val Arg Pro
210 215 220

Leu Pro Pro Trp Asp Ile Arg Ile Lys Phe Gln Lys Ala Ser Val Ser
225 230 235 240

Arg Cys Thr Leu Tyr Trp Arg Asp Glu Gly Leu Val Leu Leu Asn Arg
245 250 255

Leu Arg Tyr Arg Pro Ser Asn Ser Arg Leu Trp Asn Met Val Asn Val
260 265 270

Thr Lys Ala Lys Gly Arg His Asp Leu Leu Asp Leu Lys Pro Phe Thr
275 280 285

Glu Tyr Glu Phe Gln Ile Ser Ser Lys Leu His Leu Tyr Lys Gly Ser
290 295 300

Trp Ser Asp Trp Ser Glu Ser Leu Arg Ala Gln Thr Pro Glu Glu Glu
305 310 315 320

Pro Thr Gly Met Leu Asp Val Trp Tyr Met Lys Arg His Ile Asp Tyr
325 330 335

Ser Arg Gln Gln Ile Ser Leu Phe Trp Lys Asn Leu Ser Val Ser Glu
340 345 350

Ala Arg Gly Lys Ile Leu His Tyr Gln Val Thr Leu Gln Glu Leu Thr
355 360 365

Gly Gly Lys Ala Met Thr Gln Asn Ile Thr Gly His Thr Ser Trp Thr
370 375 380

Thr Val Ile Pro Arg Thr Gly Asn Trp Ala Val Ala Val Ser Ala Ala
385 390 395 400

Asn Ser Lys Gly Ser Ser Leu Pro Thr Arg Ile Asn Ile Met Asn Leu
405 410 415

Cys Glu Ala Gly Leu Leu Ala Pro Arg Gln Val Ser Ala Asn Ser Glu
420 425 430

Gly Met Asp Asn Ile Leu Val Thr Trp Gln Pro Pro Arg Lys Asp Pro
435 440 445

Ser Ala Val Gln Glu Tyr Val Val Glu Trp Arg Glu Leu His Pro Gly
450 455 460

Gly Asp Thr Gln Val Pro Leu Asn Trp Leu Arg Ser Arg Pro Tyr Asn
465 470 475 480

Val Ser Ala Leu Ile Ser Glu Asn Ile Lys Ser Tyr Ile Cys Tyr Glu
485 490 495

Ile Arg Val Tyr Ala Leu Ser Gly Asp Gln Gly Gly Cys Ser Ser Ile

500

505

510

Leu Gly Asn Ser Lys His Lys Ala Pro Leu Ser Gly Pro His Ile Asn
515 520 525

Ala Ile Thr Glu Glu Lys Gly Ser Ile Leu Ile Ser Trp Asn Ser Ile
530 535 540

Pro Val Gln Glu Gln Met Gly Cys Leu Leu His Tyr Arg Ile Tyr Trp
545 550 555 560

Lys Glu Arg Asp Ser Asn Ser Gln Pro Gln Leu Cys Glu Ile Pro Tyr
565 570 575

Arg Val Ser Gln Asn Ser His Pro Ile Asn Ser Leu Gln Pro Arg Val
580 585 590

Thr Tyr Val Leu Trp Met Thr Ala Leu Thr Ala Ala Gly Glu Ser Ser
595 600 605

His Gly Asn Glu Arg Glu Phe Cys Leu Gln Gly Lys Ala Asn Trp Met
610 615 620

Ala Phe Val Ala Pro Ser Ile Cys Ile Ala Ile Ile Met Val Gly Ile
625 630 635 640

Phe Ser Thr His Tyr Phe Gln Gln Lys Val Phe Val Leu Leu Ala Ala
645 650 655

Leu Arg Pro Gln Trp Cys Ser Arg Glu Ile Pro Asp Pro Ala Asn Ser
660 665 670

Thr Cys Ala Lys Lys Tyr Pro Ile Ala Glu Glu Lys Thr Gln Leu Pro
675 680 685

Leu Asp Arg Leu Leu Ile Asp Trp Pro Thr Pro Glu Asp Pro Glu Pro
690 695 700

Leu Val Ile Ser Glu Val Leu His Gln Val Thr Pro Val Phe Arg His
705 710 715 720

Pro Pro Cys Ser Asn Trp Pro Gln Arg Glu Lys Gly Ile Gln Gly His
725 730 735

Gln Ala Ser Glu Lys Asp Met Met His Ser Ala Ser Ser Pro Pro Pro
740 745 750

Pro Arg Ala Leu Gln Ala Glu Ser Arg Gln Leu Val Asp Leu Tyr Lys
755 760 765

Val Leu Glu Ser Arg Gly Ser Asp Pro Lys Pro Glu Asn Pro Ala Cys
770 775 780

Pro Trp Thr Val Leu Pro Ala Gly Asp Leu Pro Thr His Asp Gly Tyr
785 790 795 800

Leu Pro Ser Asn Ile Asp Asp Leu Pro Ser His Glu Ala Pro Leu Ala
805 810 815

Asp Ser Leu Glu Glu Leu Glu Pro Gln His Ile Ser Leu Ser Val Phe
820 825 830

Pro Ser Ser Ser Leu His Pro Leu Thr Phe Ser Cys Gly Asp Lys Leu
835 840 845

Thr Leu Asp Gln Leu Lys Met Arg Cys Asp Ser Leu Met Leu
850 855 860

<210> 55
<211> 662
<212> PRT
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
IL12Rb-1 sequence"

<400> 55
Met Glu Pro Leu Val Thr Trp Val Val Pro Leu Leu Phe Leu Phe Leu
1 5 10 15

Leu Ser Arg Gln Gly Ala Ala Cys Arg Thr Ser Glu Cys Cys Phe Gln
20 25 30

Asp Pro Pro Tyr Pro Asp Ala Asp Ser Gly Ser Ala Ser Gly Pro Arg
35 40 45

Asp Leu Arg Cys Tyr Arg Ile Ser Ser Asp Arg Tyr Glu Cys Ser Trp
50 55 60

Gln Tyr Glu Gly Pro Thr Ala Gly Val Ser His Phe Leu Arg Cys Cys
65 70 75 80

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

Leu Gln Phe Ser Asp Gln Ala Gly Val Ser Val Leu Tyr Thr Val Thr
100 105 110

Leu Trp Val Glu Ser Trp Ala Arg Asn Gln Thr Glu Lys Ser Pro Glu
115 120 125

Val Thr Leu Gln Leu Tyr Asn Ser Val Lys Tyr Glu Pro Pro Leu Gly

130

135

140

Asp Ile Lys Val Ser Lys Leu Ala Gly Gln Leu Arg Met Glu Trp Glu
 145 150 155 160

Thr Pro Asp Asn Gln Val Gly Ala Glu Val Gln Phe Arg His Arg Thr
 165 170 175

Pro Ser Ser Pro Trp Lys Leu Gly Asp Cys Gly Pro Gln Asp Asp Asp
 180 185 190

Thr Glu Ser Cys Leu Cys Pro Leu Glu Met Asn Val Ala Gln Glu Phe
 195 200 205

Gln Leu Arg Arg Arg Gln Leu Gly Ser Gln Gly Ser Ser Trp Ser Lys
 210 215 220

Trp Ser Ser Pro Val Cys Val Pro Pro Glu Asn Pro Pro Gln Pro Gln
 225 230 235 240

Val Arg Phe Ser Val Glu Gln Leu Gly Gln Asp Gly Arg Arg Arg Leu
 245 250 255

Thr Leu Lys Glu Gln Pro Thr Gln Leu Glu Leu Pro Glu Gly Cys Gln
 260 265 270

Gly Leu Ala Pro Gly Thr Glu Val Thr Tyr Arg Leu Gln Leu His Met
 275 280 285

Leu Ser Cys Pro Cys Lys Ala Lys Ala Thr Arg Thr Leu His Leu Gly
 290 295 300

Lys Met Pro Tyr Leu Ser Gly Ala Ala Tyr Asn Val Ala Val Ile Ser
 305 310 315 320

Ser Asn Gln Phe Gly Pro Gly Leu Asn Gln Thr Trp His Ile Pro Ala
325 330 335

Asp Thr His Thr Glu Pro Val Ala Leu Asn Ile Ser Val Gly Thr Asn
340 345 350

Gly Thr Thr Met Tyr Trp Pro Ala Arg Ala Gln Ser Met Thr Tyr Cys
355 360 365

Ile Glu Trp Gln Pro Val Gly Gln Asp Gly Gly Leu Ala Thr Cys Ser
370 375 380

Leu Thr Ala Pro Gln Asp Pro Asp Pro Ala Gly Met Ala Thr Tyr Ser
385 390 395 400

Trp Ser Arg Glu Ser Gly Ala Met Gly Gln Glu Lys Cys Tyr Tyr Ile
405 410 415

Thr Ile Phe Ala Ser Ala His Pro Glu Lys Leu Thr Leu Trp Ser Thr
420 425 430

Val Leu Ser Thr Tyr His Phe Gly Gly Asn Ala Ser Ala Ala Gly Thr
435 440 445

Pro His His Val Ser Val Lys Asn His Ser Leu Asp Ser Val Ser Val
450 455 460

Asp Trp Ala Pro Ser Leu Leu Ser Thr Cys Pro Gly Val Leu Lys Glu
465 470 475 480

Tyr Val Val Arg Cys Arg Asp Glu Asp Ser Lys Gln Val Ser Glu His
485 490 495

Pro Val Gln Pro Thr Glu Thr Gln Val Thr Leu Ser Gly Leu Arg Ala
500 505 510

Gly Val Ala Tyr Thr Val Gln Val Arg Ala Asp Thr Ala Trp Leu Arg
515 520 525

Gly Val Trp Ser Gln Pro Gln Arg Phe Ser Ile Glu Val Gln Val Ser
530 535 540

Asp Trp Leu Ile Phe Phe Ala Ser Leu Gly Ser Phe Leu Ser Ile Leu
545 550 555 560

Leu Val Gly Val Leu Gly Tyr Leu Gly Leu Asn Arg Ala Ala Arg His
565 570 575

Leu Cys Pro Pro Leu Pro Thr Pro Cys Ala Ser Ser Ala Ile Glu Phe
580 585 590

Pro Gly Gly Lys Glu Thr Trp Gln Trp Ile Asn Pro Val Asp Phe Gln
595 600 605

Glu Glu Ala Ser Leu Gln Glu Ala Leu Val Val Glu Met Ser Trp Asp
610 615 620

Lys Gly Glu Arg Thr Glu Pro Leu Glu Lys Thr Glu Leu Pro Glu Gly
625 630 635 640

Ala Pro Glu Leu Ala Leu Asp Thr Glu Leu Ser Leu Glu Asp Gly Asp
645 650 655

Arg Cys Lys Ala Lys Met
660

<210> 56
<211> 328
<212> PRT
<213> Homo sapiens

<400> 56

Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

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

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser
325

<210> 57

<211> 335

<212> PRT

<213> Mus musculus

<400> 57

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

Val Ser Pro Leu Met Ala Met Trp Glu Leu Glu Lys Asp Val Tyr Val
20 25 30

Val Glu Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr Val Asn Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr Ser Asp Gln
50 55 60

Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr Val Lys
65 70 75 80

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

Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly Ile Trp
100 105 110

Ser Thr Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe Leu Lys Cys
115 120 125

Glu Ala Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp Leu Val Gln
130 135 140

Arg Asn Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser Ser Ser Pro
145 150 155 160

Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser Ala Glu Lys
165 170 175

Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val Ser Cys Gln
180 185 190

Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro Ile Glu Leu
195 200 205

Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr Ser Thr Ser
210 215 220

Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
225 230 235 240

Met Lys Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp Glu Tyr Pro
245 250 255

Asp Ser Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys Phe Phe Val
260 265 270

Arg Ile Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu Glu Gly Cys
275 280 285

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

Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr Tyr Asn
305 310 315 320

Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg Ser
325 330 335

<210> 58
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 58
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
65 70 75 80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

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

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Val Gly Ala Phe Arg Pro Tyr
115 120 125

Arg Lys His Glu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Arg Gly
130 135 140

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

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
165 170 175

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
195 200 205

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
210 215 220

Gly Asn Thr Ala Ser Leu Thr Thr Thr Gly Ala Gln Ala Glu Asp Glu
225 230 235 240

Ala Asp Tyr Tyr Cys Asn Ser Ser Pro Phe Glu His Asn Leu Val Val
245 250 255

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu His His His His His His
260 265 270

Glu Pro Glu Ala
275

<210> 59

<211> 549

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 59

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Arg Val Ile Pro Val Ser Gly Pro Ala Arg
20 25 30

Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val
35 40 45

Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu Asp
50 55 60

Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr
65 70 75 80

Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg
85 90 95

Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr
100 105 110

Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys
115 120 125

Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His
130 135 140

Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp
145 150 155 160

Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys

165

170

175

Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys
 180 185 190

Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val
 195 200 205

Met Gly Tyr Leu Ser Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly Met
 210 215 220

Lys Gly Leu Pro Gly Ser Met Trp Glu Leu Glu Lys Asp Val Tyr Val
 225 230 235 240

Val Glu Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr Val Asn Leu
 245 250 255

Thr Cys Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr Ser Asp Gln
 260 265 270

Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr Val Lys
 275 280 285

Glu Phe Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Thr
 290 295 300

Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly Ile Trp
 305 310 315 320

Ser Thr Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe Leu Lys Cys
 325 330 335

Glu Ala Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp Leu Val Gln
 340 345 350

Arg Asn Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser Ser Ser Pro
355 360 365

Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser Ala Glu Lys
370 375 380

Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val Ser Cys Gln
385 390 395 400

Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro Ile Glu Leu
405 410 415

Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr Ser Thr Ser
420 425 430

Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln
435 440 445

Met Lys Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp Glu Tyr Pro
450 455 460

Asp Ser Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys Phe Phe Val
465 470 475 480

Arg Ile Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu Glu Gly Cys
485 490 495

Asn Gln Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr Glu Val Gln
500 505 510

Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr Tyr Asn
515 520 525

Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg Ser His
530 535 540

His His His His His
545

<210> 60

<211> 579

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 60

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Arg Val Ile Pro Val Ser Gly Pro Ala Arg
20 25 30

Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val
35 40 45

Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu Asp
50 55 60

Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr
65 70 75 80

Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg
85 90 95

Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr

100

105

110

Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys
 115 120 125

Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His
 130 135 140

Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp
 145 150 155 160

Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys
 165 170 175

Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys
 180 185 190

Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val
 195 200 205

Met Gly Tyr Leu Ser Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
 210 215 220

Ser Gly Gly Gly Gly Ser Ser Gly Gly Pro Gly Pro Ala Gly Met Lys
 225 230 235 240

Gly Leu Pro Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 245 250 255

Gly Gly Gly Ser Met Trp Glu Leu Glu Lys Asp Val Tyr Val Val Glu
 260 265 270

Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr Val Asn Leu Thr Cys
 275 280 285

Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr Ser Asp Gln Arg His
290 295 300

Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr Val Lys Glu Phe
305 310 315 320

Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Thr Leu Ser
325 330 335

His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly Ile Trp Ser Thr
340 345 350

Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe Leu Lys Cys Glu Ala
355 360 365

Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp Leu Val Gln Arg Asn
370 375 380

Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser Ser Pro Asp Ser
385 390 395 400

Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser Ala Glu Lys Val Thr
405 410 415

Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val Ser Cys Gln Glu Asp
420 425 430

Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro Ile Glu Leu Ala Leu
435 440 445

Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr Ser Thr Ser Phe Phe
450 455 460

Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn Leu Gln Met Lys
465 470 475 480

Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp Glu Tyr Pro Asp Ser
485 490 495

Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys Phe Phe Val Arg Ile
500 505 510

Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu Glu Gly Cys Asn Gln
515 520 525

Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr Glu Val Gln Cys Lys
530 535 540

Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr Tyr Asn Ser Ser
545 550 555 560

Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg Ser His His His
565 570 575

His His His

<210> 61

<211> 809

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 61

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1		5		10		15											
Leu	Arg	Gly	Ala	Arg	Cys	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly		
		20						25					30				
Leu	Val	Gln	Pro	Gly	Asn	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly		
		35					40					45					
Phe	Thr	Phe	Ser	Lys	Phe	Gly	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly		
	50					55					60						
Lys	Gly	Leu	Glu	Trp	Val	Ser	Ser	Ile	Ser	Gly	Ser	Gly	Arg	Asp	Thr		
65					70					75					80		
Leu	Tyr	Ala	Glu	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn		
				85					90					95			
Ala	Lys	Thr	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Glu	Asp		
			100					105					110				
Thr	Ala	Val	Tyr	Tyr	Cys	Thr	Ile	Gly	Gly	Ser	Leu	Ser	Val	Ser	Ser		
		115					120					125					
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ser	Gly	Gly	Pro	Gly	Pro	Ala		
	130					135					140						
Gly	Met	Lys	Gly	Leu	Pro	Gly	Ser	Met	Trp	Glu	Leu	Glu	Lys	Asp	Val		
145					150					155					160		
Tyr	Val	Val	Glu	Val	Asp	Trp	Thr	Pro	Asp	Ala	Pro	Gly	Glu	Thr	Val		
				165					170					175			
Asn	Leu	Thr	Cys	Asp	Thr	Pro	Glu	Glu	Asp	Asp	Ile	Thr	Trp	Thr	Ser		
			180					185					190				

Asp Gln Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr
195 200 205

Val Lys Glu Phe Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly
210 215 220

Glu Thr Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly
225 230 235 240

Ile Trp Ser Thr Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe Leu
245 250 255

Lys Cys Glu Ala Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp Leu
260 265 270

Val Gln Arg Asn Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser Ser
275 280 285

Ser Pro Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser Ala
290 295 300

Glu Lys Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val Ser
305 310 315 320

Cys Gln Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro Ile
325 330 335

Glu Leu Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr Ser
340 345 350

Thr Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
355 360 365

Leu Gln Met Lys Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp Glu
370 375 380

Tyr Pro Asp Ser Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys Phe
385 390 395 400

Phe Val Arg Ile Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu Glu
405 410 415

Gly Cys Asn Gln Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr Glu
420 425 430

Val Gln Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr
435 440 445

Tyr Asn Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg
450 455 460

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser Arg
485 490 495

Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu Lys
500 505 510

Leu Lys His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp Ile
515 520 525

Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu Leu
530 535 540

His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr Thr
545 550 555 560

Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr Leu
565 570 575

Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu Phe
580 585 590

Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile Ile
595 600 605

Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser Leu
610 615 620

Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu Ala
625 630 635 640

Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe
645 650 655

Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser
660 665 670

Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser
675 680 685

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
690 695 700

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
705 710 715 720

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

725

730

735

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val
740 745 750

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
755 760 765

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
770 775 780

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
785 790 795 800

Val Ser Ser His His His His His His
805

<210> 62

<211> 938

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 62

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Leu Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Arg Ile Phe Ser Ile Asp Ile Met Ser Trp Tyr Arg Gln Ala Pro Gly
50 55 60

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

Tyr Asp Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr
100 105 110

Gly Val Tyr Tyr Cys Asn Ala Leu Tyr Gly Thr Asp Tyr Trp Gly Lys
115 120 125

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

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

Gly Leu Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser
165 170 175

Gly Phe Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro
180 185 190

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

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

Asn	Ala	Lys	Thr	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Glu
225					230					235					240
Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Thr	Ile	Gly	Gly	Ser	Leu	Ser	Val	Ser
				245					250					255	
Ser	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ser	Gly	Gly	Pro	Gly	Pro
			260					265					270		
Ala	Gly	Met	Lys	Gly	Leu	Pro	Gly	Ser	Met	Trp	Glu	Leu	Glu	Lys	Asp
		275					280					285			
Val	Tyr	Val	Val	Glu	Val	Asp	Trp	Thr	Pro	Asp	Ala	Pro	Gly	Glu	Thr
	290					295					300				
Val	Asn	Leu	Thr	Cys	Asp	Thr	Pro	Glu	Glu	Asp	Asp	Ile	Thr	Trp	Thr
305					310					315					320
Ser	Asp	Gln	Arg	His	Gly	Val	Ile	Gly	Ser	Gly	Lys	Thr	Leu	Thr	Ile
				325					330					335	
Thr	Val	Lys	Glu	Phe	Leu	Asp	Ala	Gly	Gln	Tyr	Thr	Cys	His	Lys	Gly
			340					345					350		
Gly	Glu	Thr	Leu	Ser	His	Ser	His	Leu	Leu	Leu	His	Lys	Lys	Glu	Asn
		355					360					365			
Gly	Ile	Trp	Ser	Thr	Glu	Ile	Leu	Lys	Asn	Phe	Lys	Asn	Lys	Thr	Phe
	370					375					380				
Leu	Lys	Cys	Glu	Ala	Pro	Asn	Tyr	Ser	Gly	Arg	Phe	Thr	Cys	Ser	Trp
385					390					395					400
Leu	Val	Gln	Arg	Asn	Met	Asp	Leu	Lys	Phe	Asn	Ile	Lys	Ser	Ser	Ser

405

410

415

Ser Ser Pro Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser
 420 425 430

Ala Glu Lys Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val
 435 440 445

Ser Cys Gln Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro
 450 455 460

Ile Glu Leu Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr
 465 470 475 480

Ser Thr Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys
 485 490 495

Asn Leu Gln Met Lys Pro Leu Lys Asn Ser Gln Val Glu Val Ser Trp
 500 505 510

Glu Tyr Pro Asp Ser Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Lys
 515 520 525

Phe Phe Val Arg Ile Gln Arg Lys Lys Glu Lys Met Lys Glu Thr Glu
 530 535 540

Glu Gly Cys Asn Gln Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr
 545 550 555 560

Glu Val Gln Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg
 565 570 575

Tyr Tyr Asn Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val
 580 585 590

Arg Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
595 600 605

Ser Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser
610 615 620

Arg Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu
625 630 635 640

Lys Leu Lys His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp
645 650 655

Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu
660 665 670

Leu His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr
675 680 685

Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr
690 695 700

Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu
705 710 715 720

Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile
725 730 735

Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser
740 745 750

Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu
755 760 765

Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala
770 775 780

Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser
785 790 795 800

Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly
805 810 815

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
820 825 830

Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys
835 840 845

Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
850 855 860

Val Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser
865 870 875 880

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu
885 890 895

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
900 905 910

Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val
915 920 925

Thr Val Ser Ser His His His His His His
930 935

<210> 63
<211> 938
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 63
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Leu Val Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Arg Ile Phe Ser Ile Asp Ile Met Ser Trp Tyr Arg Gln Ala Pro Gly
50 55 60

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

Tyr Asp Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr
100 105 110

Gly Val Tyr Tyr Cys Asn Ala Leu Tyr Gly Thr Asp Tyr Trp Gly Lys
115 120 125

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

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

Gly Leu Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser
165 170 175

Gly Phe Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro
180 185 190

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

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

Asn Ala Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu
225 230 235 240

Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser Val Ser
245 250 255

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

Ala Gly Met Lys Gly Leu Pro Gly Ser Met Trp Glu Leu Glu Lys Asp
275 280 285

Val Tyr Val Val Glu Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr
290 295 300

Val Asn Leu Thr Cys Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr
305 310 315 320

Ser Asp Gln Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile
325 330 335

Thr Val Lys Glu Phe Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly
340 345 350

Gly Glu Thr Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn
355 360 365

Gly Ile Trp Ser Thr Glu Ile Leu Lys Asn Phe Lys Asn Lys Thr Phe
370 375 380

Leu Lys Cys Glu Ala Pro Asn Tyr Ser Gly Arg Phe Thr Cys Ser Trp
385 390 395 400

Leu Val Gln Arg Asn Met Asp Leu Lys Phe Asn Ile Lys Ser Ser Ser
405 410 415

Ser Ser Pro Asp Ser Arg Ala Val Thr Cys Gly Met Ala Ser Leu Ser
420 425 430

Ala Glu Lys Val Thr Leu Asp Gln Arg Asp Tyr Glu Lys Tyr Ser Val
435 440 445

Ser Cys Gln Glu Asp Val Thr Cys Pro Thr Ala Glu Glu Thr Leu Pro
450 455 460

Ile Glu Leu Ala Leu Glu Ala Arg Gln Gln Asn Lys Tyr Glu Asn Tyr
465 470 475 480

Ser Thr Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys
485 490 495

Asn	Leu	Gln	Met	Lys	Pro	Leu	Lys	Asn	Ser	Gln	Val	Glu	Val	Ser	Trp
			500					505					510		
Glu	Tyr	Pro	Asp	Ser	Trp	Ser	Thr	Pro	His	Ser	Tyr	Phe	Ser	Leu	Lys
		515					520					525			
Phe	Phe	Val	Arg	Ile	Gln	Arg	Lys	Lys	Glu	Lys	Met	Lys	Glu	Thr	Glu
	530					535					540				
Glu	Gly	Cys	Asn	Gln	Lys	Gly	Ala	Phe	Leu	Val	Glu	Lys	Thr	Ser	Thr
545					550					555					560
Glu	Val	Gln	Cys	Lys	Gly	Gly	Asn	Val	Cys	Val	Gln	Ala	Gln	Asp	Arg
				565					570					575	
Tyr	Tyr	Asn	Ser	Ser	Cys	Ser	Lys	Trp	Ala	Cys	Val	Pro	Cys	Arg	Val
			580					585					590		
Arg	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
		595					600					605			
Ser	Arg	Val	Ile	Pro	Val	Ser	Gly	Pro	Ala	Arg	Cys	Leu	Ser	Gln	Ser
	610					615					620				
Arg	Asn	Leu	Leu	Lys	Thr	Thr	Asp	Asp	Met	Val	Lys	Thr	Ala	Arg	Glu
625					630					635					640
Lys	Leu	Lys	His	Tyr	Ser	Cys	Thr	Ala	Glu	Asp	Ile	Asp	His	Glu	Asp
				645					650					655	
Ile	Thr	Arg	Asp	Gln	Thr	Ser	Thr	Leu	Lys	Thr	Cys	Leu	Pro	Leu	Glu
			660					665					670		
Leu	His	Lys	Asn	Glu	Ser	Cys	Leu	Ala	Thr	Arg	Glu	Thr	Ser	Ser	Thr

675

680

685

Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr
 690 695 700

Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu
 705 710 715 720

Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile
 725 730 735

Ile Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser
 740 745 750

Leu Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu
 755 760 765

Ala Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala
 770 775 780

Phe Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser
 785 790 795 800

Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly
 805 810 815

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 820 825 830

Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys
 835 840 845

Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 850 855 860

Val Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser
865 870 875 880

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu
885 890 895

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
900 905 910

Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val
915 920 925

Thr Val Ser Ser His His His His His His
930 935

<210> 64

<211> 938

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 64

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
1 5 10 15

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

Leu Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr
65 70 75 80

Leu Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ala Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser
115 120 125

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

Gly Met Lys Gly Leu Pro Gly Ser Met Trp Glu Leu Glu Lys Asp Val
145 150 155 160

Tyr Val Val Glu Val Asp Trp Thr Pro Asp Ala Pro Gly Glu Thr Val
165 170 175

Asn Leu Thr Cys Asp Thr Pro Glu Glu Asp Asp Ile Thr Trp Thr Ser
180 185 190

Asp Gln Arg His Gly Val Ile Gly Ser Gly Lys Thr Leu Thr Ile Thr
195 200 205

Val Lys Glu Phe Leu Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly
210 215 220

Glu Thr Leu Ser His Ser His Leu Leu Leu His Lys Lys Glu Asn Gly

225						230						235						240
Ile	Trp	Ser	Thr	Glu	Ile	Leu	Lys	Asn	Phe	Lys	Asn	Lys	Thr	Phe	Leu			
				245					250					255				
Lys	Cys	Glu	Ala	Pro	Asn	Tyr	Ser	Gly	Arg	Phe	Thr	Cys	Ser	Trp	Leu			
				260					265					270				
Val	Gln	Arg	Asn	Met	Asp	Leu	Lys	Phe	Asn	Ile	Lys	Ser	Ser	Ser	Ser			
				275					280					285				
Ser	Pro	Asp	Ser	Arg	Ala	Val	Thr	Cys	Gly	Met	Ala	Ser	Leu	Ser	Ala			
				290					295					300				
Glu	Lys	Val	Thr	Leu	Asp	Gln	Arg	Asp	Tyr	Glu	Lys	Tyr	Ser	Val	Ser			
				305					310					315				
Cys	Gln	Glu	Asp	Val	Thr	Cys	Pro	Thr	Ala	Glu	Glu	Thr	Leu	Pro	Ile			
				325					330					335				
Glu	Leu	Ala	Leu	Glu	Ala	Arg	Gln	Gln	Asn	Lys	Tyr	Glu	Asn	Tyr	Ser			
				340					345					350				
Thr	Ser	Phe	Phe	Ile	Arg	Asp	Ile	Ile	Lys	Pro	Asp	Pro	Pro	Lys	Asn			
				355					360					365				
Leu	Gln	Met	Lys	Pro	Leu	Lys	Asn	Ser	Gln	Val	Glu	Val	Ser	Trp	Glu			
				370					375					380				
Tyr	Pro	Asp	Ser	Trp	Ser	Thr	Pro	His	Ser	Tyr	Phe	Ser	Leu	Lys	Phe			
				385					390					395				
Phe	Val	Arg	Ile	Gln	Arg	Lys	Lys	Glu	Lys	Met	Lys	Glu	Thr	Glu	Glu			
				405					410					415				

Gly Cys Asn Gln Lys Gly Ala Phe Leu Val Glu Lys Thr Ser Thr Glu
420 425 430

Val Gln Cys Lys Gly Gly Asn Val Cys Val Gln Ala Gln Asp Arg Tyr
435 440 445

Tyr Asn Ser Ser Cys Ser Lys Trp Ala Cys Val Pro Cys Arg Val Arg
450 455 460

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Arg Val Ile Pro Val Ser Gly Pro Ala Arg Cys Leu Ser Gln Ser Arg
485 490 495

Asn Leu Leu Lys Thr Thr Asp Asp Met Val Lys Thr Ala Arg Glu Lys
500 505 510

Leu Lys His Tyr Ser Cys Thr Ala Glu Asp Ile Asp His Glu Asp Ile
515 520 525

Thr Arg Asp Gln Thr Ser Thr Leu Lys Thr Cys Leu Pro Leu Glu Leu
530 535 540

His Lys Asn Glu Ser Cys Leu Ala Thr Arg Glu Thr Ser Ser Thr Thr
545 550 555 560

Arg Gly Ser Cys Leu Pro Pro Gln Lys Thr Ser Leu Met Met Thr Leu
565 570 575

Cys Leu Gly Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Thr Glu Phe
580 585 590

Gln Ala Ile Asn Ala Ala Leu Gln Asn His Asn His Gln Gln Ile Ile
595 600 605

Leu Asp Lys Gly Met Leu Val Ala Ile Asp Glu Leu Met Gln Ser Leu
610 615 620

Asn His Asn Gly Glu Thr Leu Arg Gln Lys Pro Pro Val Gly Glu Ala
625 630 635 640

Asp Pro Tyr Arg Val Lys Met Lys Leu Cys Ile Leu Leu His Ala Phe
645 650 655

Ser Thr Arg Val Val Thr Ile Asn Arg Val Met Gly Tyr Leu Ser Ser
660 665 670

Ala Ser Gly Gly Pro Gly Pro Ala Gly Met Lys Gly Leu Pro Gly Ser
675 680 685

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
690 695 700

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
705 710 715 720

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
725 730 735

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Glu Ser Val
740 745 750

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
755 760 765

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
770 775 780

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
785 790 795 800

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
805 810 815

Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala
820 825 830

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser
835 840 845

Ile Asp Ile Met Ser Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu
850 855 860

Leu Val Ala Arg Ile Thr Arg Gly Gly Thr Ile Ser Tyr Asp Asp Ser
865 870 875 880

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val
885 890 895

Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr Tyr
900 905 910

Cys Asn Ala Leu Tyr Gly Thr Asp Tyr Trp Gly Lys Gly Thr Gln Val
915 920 925

Thr Val Ser Ser His His His His His His
930 935

<210> 65

<211> 962

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 65

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

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

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
325 330 335

Gly Ser Gly Gly Gly Gly Ser Arg Val Ile Pro Val Ser Gly Pro Ala
340 345 350

Arg Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met
355 360 365

Val Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu
370 375 380

Asp Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys
385 390 395 400

Thr Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr
405 410 415

Arg Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys
420 425 430

Thr Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu
435 440 445

Lys Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn
450 455 460

His Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile
465 470 475 480

Asp Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln
485 490 495

Lys Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu

500

505

510

Cys Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg
 515 520 525

Val Met Gly Tyr Leu Ser Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly
 530 535 540

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 545 550 555 560

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 565 570 575

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
 580 585 590

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg Ser
 595 600 605

Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr
 610 615 620

Ala Pro Lys Leu Leu Ile Tyr Tyr Asn Asp Gln Arg Pro Ser Gly Val
 625 630 635 640

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
 645 650 655

Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
 660 665 670

Tyr Asp Arg Tyr Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys
 675 680 685

Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
690 695 700

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
705 710 715 720

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
725 730 735

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
740 745 750

Glu Trp Val Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
755 760 765

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
770 775 780

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
785 790 795 800

Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr
805 810 815

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
820 825 830

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
835 840 845

Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
850 855 860

Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys
865 870 875 880

Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu
885 890 895

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
900 905 910

Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr
915 920 925

Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln
930 935 940

Gly Thr Leu Val Thr Val Ser Ser His His His His His His Glu Pro
945 950 955 960

Glu Ala

<210> 66

<211> 832

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 66

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Ile Trp Glu Leu Lys Lys Asp Val Tyr Val

20

25

30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
 35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
 50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
 65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
 85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
 100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
 115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
 130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
 145 150 155 160

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

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
 180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
 195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
325 330 335

Gly Ser Gly Gly Gly Gly Ser Arg Val Ile Pro Val Ser Gly Pro Ala
340 345 350

Arg Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met
355 360 365

Val Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu
370 375 380

Asp Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys
385 390 395 400

Thr Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr
405 410 415

Arg Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys
420 425 430

Thr Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu
435 440 445

Lys Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn
450 455 460

His Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile
465 470 475 480

Asp Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln
485 490 495

Lys Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu
500 505 510

Cys Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg
515 520 525

Val Met Gly Tyr Leu Ser Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly
530 535 540

Met Lys Gly Leu Pro Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
545 550 555 560

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 565 570 575

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
 580 585 590

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg Ser
 595 600 605

Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr
 610 615 620

Ala Pro Lys Leu Leu Ile Tyr Tyr Asn Asp Gln Arg Pro Ser Gly Val
 625 630 635 640

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
 645 650 655

Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
 660 665 670

Tyr Asp Arg Tyr Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys
 675 680 685

Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 690 695 700

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
 705 710 715 720

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 725 730 735

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu

740

745

750

Glu Trp Val Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
755 760 765

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
770 775 780

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
785 790 795 800

Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr
805 810 815

Met Val Thr Val Ser Ser His His His His His His Glu Pro Glu Ala
820 825 830

<210> 67

<211> 1091

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 67

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val
85 90 95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
100 105 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
115 120 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
130 135 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145 150 155 160

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

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
180 185 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
195 200 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
210 215 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225 230 235 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
245 250 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
260 265 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
275 280 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
290 295 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305 310 315 320

Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly Gly
325 330 335

Gly Ser Gly Gly Gly Gly Ser Arg Val Ile Pro Val Ser Gly Pro Ala
340 345 350

Arg Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp Met
355 360 365

Val Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala Glu
370 375 380

Asp Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu Lys
385 390 395 400

Thr Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala Thr

405

410

415

Arg Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln Lys
 420 425 430

Thr Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp Leu
 435 440 445

Lys Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln Asn
 450 455 460

His Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala Ile
 465 470 475 480

Asp Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg Gln
 485 490 495

Lys Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys Leu
 500 505 510

Cys Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn Arg
 515 520 525

Val Met Gly Tyr Leu Ser Ser Ala Ser Gly Gly Pro Gly Pro Ala Gly
 530 535 540

Met Lys Gly Leu Pro Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 545 550 555 560

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 565 570 575

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
 580 585 590

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg Ser
595 600 605

Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly Thr
610 615 620

Ala Pro Lys Leu Leu Ile Tyr Tyr Asn Asp Gln Arg Pro Ser Gly Val
625 630 635 640

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
645 650 655

Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
660 665 670

Tyr Asp Arg Tyr Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr Lys
675 680 685

Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
690 695 700

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
705 710 715 720

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
725 730 735

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
740 745 750

Glu Trp Val Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
755 760 765

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
770 775 780

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
785 790 795 800

Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly Thr
805 810 815

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
820 825 830

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
835 840 845

Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
850 855 860

Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys
865 870 875 880

Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu
885 890 895

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
900 905 910

Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr
915 920 925

Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln
930 935 940

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
945 950 955 960

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly
965 970 975

Gly Leu Ala Gln Ala Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser
980 985 990

Gly Phe Thr Val Ser Asn Ser Val Met Ala Trp Tyr Arg Gln Thr Pro
995 1000 1005

Gly Lys Gln Arg Glu Phe Val Ala Ile Ile Asn Ser Val Gly Ser
1010 1015 1020

Thr Asn Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
1025 1030 1035

Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met Asn Asn Leu Lys
1040 1045 1050

Pro Glu Asp Thr Ala Val Tyr Val Cys Asn Arg Asn Phe Asp Arg
1055 1060 1065

Ile Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser His His
1070 1075 1080

His His His His Glu Pro Glu Ala
1085 1090

<210> 68

<211> 1091

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 68

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Leu Ala Gln Ala Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly
35 40 45

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

Lys Gln Arg Glu Phe Val Ala Ile Ile Asn Ser Val Gly Ser Thr Asn
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Val Tyr Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr
100 105 110

Ala Val Tyr Val Cys Asn Arg Asn Phe Asp Arg Ile Tyr Trp Gly Gln
115 120 125

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Ile Trp Glu Leu Lys Lys Asp Val Tyr
145 150 155 160

Val Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val
165 170 175

Leu Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp
180 185 190

Gln Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val
195 200 205

Lys Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu
210 215 220

Val Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile
225 230 235 240

Trp Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr
245 250 255

Phe Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp
260 265 270

Trp Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser
275 280 285

Arg Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu
290 295 300

Ser Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val
305 310 315 320

Glu Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro
325 330 335

Ile	Glu	Val	Met	Val	Asp	Ala	Val	His	Lys	Leu	Lys	Tyr	Glu	Asn	Tyr			
			340					345					350					
Thr	Ser	Ser	Phe	Phe	Ile	Arg	Asp	Ile	Ile	Lys	Pro	Asp	Pro	Pro	Lys			
		355					360					365						
Asn	Leu	Gln	Leu	Lys	Pro	Leu	Lys	Asn	Ser	Arg	Gln	Val	Glu	Val	Ser			
	370					375					380							
Trp	Glu	Tyr	Pro	Asp	Thr	Trp	Ser	Thr	Pro	His	Ser	Tyr	Phe	Ser	Leu			
385					390					395					400			
Thr	Phe	Cys	Val	Gln	Val	Gln	Gly	Lys	Ser	Lys	Arg	Glu	Lys	Lys	Asp			
				405					410					415				
Arg	Val	Phe	Thr	Asp	Lys	Thr	Ser	Ala	Thr	Val	Ile	Cys	Arg	Lys	Asn			
			420					425					430					
Ala	Ser	Ile	Ser	Val	Arg	Ala	Gln	Asp	Arg	Tyr	Tyr	Ser	Ser	Ser	Trp			
		435					440					445						
Ser	Glu	Trp	Ala	Ser	Val	Pro	Cys	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly			
	450					455					460							
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Arg	Val	Ile	Pro	Val	Ser	Gly	Pro			
465					470					475					480			
Ala	Arg	Cys	Leu	Ser	Gln	Ser	Arg	Asn	Leu	Leu	Lys	Thr	Thr	Asp	Asp			
				485					490					495				
Met	Val	Lys	Thr	Ala	Arg	Glu	Lys	Leu	Lys	His	Tyr	Ser	Cys	Thr	Ala			
			500					505					510					
Glu	Asp	Ile	Asp	His	Glu	Asp	Ile	Thr	Arg	Asp	Gln	Thr	Ser	Thr	Leu			

515

520

525

Lys Thr Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala
 530 535 540

Thr Arg Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln
 545 550 555 560

Lys Thr Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp
 565 570 575

Leu Lys Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln
 580 585 590

Asn His Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala
 595 600 605

Ile Asp Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg
 610 615 620

Gln Lys Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys
 625 630 635 640

Leu Cys Ile Leu Leu His Ala Phe Ser Thr Arg Val Val Thr Ile Asn
 645 650 655

Arg Val Met Gly Tyr Leu Ser Ser Ala Ser Gly Gly Pro Gly Pro Ala
 660 665 670

Gly Met Lys Gly Leu Pro Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 675 680 685

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 690 695 700

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
705 710 715 720

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg
725 730 735

Ser Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly
740 745 750

Thr Ala Pro Lys Leu Leu Ile Tyr Tyr Asn Asp Gln Arg Pro Ser Gly
755 760 765

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
770 775 780

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
785 790 795 800

Ser Tyr Asp Arg Tyr Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr
805 810 815

Lys Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
820 825 830

Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val
835 840 845

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
850 855 860

Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
865 870 875 880

Leu Glu Trp Val Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr
885 890 895

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
900 905 910

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
915 920 925

Val Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly
930 935 940

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
945 950 955 960

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly
965 970 975

Leu Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
980 985 990

Phe Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly
995 1000 1005

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Arg Asp
1010 1015 1020

Thr Leu Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
1025 1030 1035

Asp Asn Ala Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
1040 1045 1050

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu
1055 1060 1065

Ser Val Ser Ser Gln Gly Thr Leu Val Thr Val Ser Ser His His
1070 1075 1080

His His His His Glu Pro Glu Ala
1085 1090

<210> 69

<211> 1091

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 69

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
1 5 10 15

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

Leu Ala Gln Ala Gly Gly Ser Leu Ser Leu Ser Cys Ala Ala Ser Gly
35 40 45

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

Lys Gln Arg Glu Phe Val Ala Ile Ile Asn Ser Val Gly Ser Thr Asn
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Thr Val Tyr Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr
100 105 110

Ala Val Tyr Val Cys Asn Arg Asn Phe Asp Arg Ile Tyr Trp Gly Gln
115 120 125

Gly Thr Gln Val Thr Val Ser Ser Ser Gly Gly Pro Gly Pro Ala Gly
130 135 140

Met Lys Gly Leu Pro Gly Ser Ile Trp Glu Leu Lys Lys Asp Val Tyr
145 150 155 160

Val Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val
165 170 175

Leu Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp
180 185 190

Gln Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val
195 200 205

Lys Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu
210 215 220

Val Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile
225 230 235 240

Trp Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr
245 250 255

Phe Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp
260 265 270

Trp Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser
275 280 285

Arg Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu
290 295 300

Ser Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val
305 310 315 320

Glu Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro
325 330 335

Ile Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr
340 345 350

Thr Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys
355 360 365

Asn Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser
370 375 380

Trp Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu
385 390 395 400

Thr Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp
405 410 415

Arg Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn
420 425 430

Ala Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp
435 440 445

Ser Glu Trp Ala Ser Val Pro Cys Ser Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Arg Val Ile Pro Val Ser Gly Pro
465 470 475 480

Ala Arg Cys Leu Ser Gln Ser Arg Asn Leu Leu Lys Thr Thr Asp Asp
485 490 495

Met Val Lys Thr Ala Arg Glu Lys Leu Lys His Tyr Ser Cys Thr Ala
500 505 510

Glu Asp Ile Asp His Glu Asp Ile Thr Arg Asp Gln Thr Ser Thr Leu
515 520 525

Lys Thr Cys Leu Pro Leu Glu Leu His Lys Asn Glu Ser Cys Leu Ala
530 535 540

Thr Arg Glu Thr Ser Ser Thr Thr Arg Gly Ser Cys Leu Pro Pro Gln
545 550 555 560

Lys Thr Ser Leu Met Met Thr Leu Cys Leu Gly Ser Ile Tyr Glu Asp
565 570 575

Leu Lys Met Tyr Gln Thr Glu Phe Gln Ala Ile Asn Ala Ala Leu Gln
580 585 590

Asn His Asn His Gln Gln Ile Ile Leu Asp Lys Gly Met Leu Val Ala
595 600 605

Ile Asp Glu Leu Met Gln Ser Leu Asn His Asn Gly Glu Thr Leu Arg
610 615 620

Gln Lys Pro Pro Val Gly Glu Ala Asp Pro Tyr Arg Val Lys Met Lys

625					630					635				640	
Leu	Cys	Ile	Leu	Leu	His	Ala	Phe	Ser	Thr	Arg	Val	Val	Thr	Ile	Asn
				645					650					655	
Arg	Val	Met	Gly	Tyr	Leu	Ser	Ser	Ala	Ser	Gly	Gly	Pro	Gly	Pro	Ala
			660					665					670		
Gly	Met	Lys	Gly	Leu	Pro	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
		675					680					685			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
	690					695					700				
Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val
705					710					715					720
Ser	Gly	Ala	Pro	Gly	Gln	Arg	Val	Thr	Ile	Ser	Cys	Ser	Gly	Ser	Arg
				725					730					735	
Ser	Asn	Ile	Gly	Ser	Asn	Thr	Val	Lys	Trp	Tyr	Gln	Gln	Leu	Pro	Gly
			740					745					750		
Thr	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Tyr	Asn	Asp	Gln	Arg	Pro	Ser	Gly
		755					760					765			
Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Thr	Ser	Ala	Ser	Leu
		770				775					780				
Ala	Ile	Thr	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln
785					790					795					800
Ser	Tyr	Asp	Arg	Tyr	Thr	His	Pro	Ala	Leu	Leu	Phe	Gly	Thr	Gly	Thr
				805					810					815	

Lys Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
820 825 830

Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val
835 840 845

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
850 855 860

Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
865 870 875 880

Leu Glu Trp Val Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr
885 890 895

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
900 905 910

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
915 920 925

Val Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly
930 935 940

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
945 950 955 960

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly
965 970 975

Leu Val Gln Pro Gly Asn Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
980 985 990

Phe Thr Phe Ser Lys Phe Gly Met Ser Trp Val Arg Gln Ala Pro Gly
995 1000 1005

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Arg Asp
1010 1015 1020

Thr Leu Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
1025 1030 1035

Asp Asn Ala Lys Thr Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
1040 1045 1050

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu
1055 1060 1065

Ser Val Ser Ser Gln Gly Thr Leu Val Thr Val Ser Ser His His
1070 1075 1080

His His His His Glu Pro Glu Ala
1085 1090

<210> 70

<211> 276

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 70

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly

20

25

30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
 35 40 45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
 50 55 60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
 65 70 75 80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
 85 90 95

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

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Val Gly Ala Phe Arg Pro Tyr
 115 120 125

Arg Lys His Glu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Arg Gly
 130 135 140

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

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
 165 170 175

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
 180 185 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
 195 200 205

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
210 215 220

Gly Asn Thr Ala Ser Leu Thr Thr Thr Gly Ala Gln Ala Glu Asp Glu
225 230 235 240

Ala Asp Tyr Tyr Cys Asn Ser Ser Pro Phe Glu His Asn Leu Val Val
245 250 255

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu His His His His His His
260 265 270

Glu Pro Glu Ala
275

<210> 71

<211> 534

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 71

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

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

Gly Met Ser Trp Val Arg Gln Gly Gly Gly Gly Gly Leu Asp Gly Asn
35 40 45

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

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

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

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser
100 105 110

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

Lys Pro Leu Gly Leu Gln Ala Arg Val Val Gly Gly Gly Gly Thr Gln
130 135 140

Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr
145 150 155 160

Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly Asn
165 170 175

Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu
180 185 190

Ile Gly Gly Thr Lys Phe Leu Val Pro Gly Thr Pro Ala Arg Phe Ser
195 200 205

Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln
210 215 220

Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Thr Leu Trp Tyr Ser Asn Arg

225					230					235				240		
Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gly	Gly	Gly	
				245					250					255		
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Val	Gln	Leu	Val	
			260					265					270			
Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	Ser	Leu	Lys	Leu	Ser	
		275					280					285				
Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	Ala	Ile	Asn	Trp	Val	
	290					295					300					
Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Arg	Ile	Arg	Ser	
305					310					315					320	
Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	Gln	Val	Lys	Asp	Arg	
				325					330					335		
Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	Ala	Tyr	Leu	Gln	Met	
			340					345					350			
Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Val	Arg	His	
		355					360					365				
Ala	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	Ala	Tyr	Trp	Gly	Gln	
	370					375					380					
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	
385					390					395					400	
Ser	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	
				405					410					415		

Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser
420 425 430

Tyr Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
435 440 445

Val Val Ala Ile Asn Trp Ala Ser Gly Ser Thr Tyr Tyr Ala Asp Ser
450 455 460

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
465 470 475 480

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
485 490 495

Cys Ala Ala Gly Tyr Gln Ile Asn Ser Gly Asn Tyr Asn Phe Lys Asp
500 505 510

Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
515 520 525

His His His His His His
530

<210> 72

<211> 534

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 72

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

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

Gly Met Ser Trp Val Arg Gln Gly Gly Gly Gly Gly Leu Asp Gly Asn
35 40 45

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

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

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

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser
100 105 110

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

Ser Gly Gly Gly Gly Ser Gly Gly Val Val Gly Gly Gly Gly Thr Gln
130 135 140

Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr
145 150 155 160

Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly Asn
165 170 175

Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu

180

185

190

Ile Gly Gly Thr Lys Phe Leu Val Pro Gly Thr Pro Ala Arg Phe Ser
195 200 205

Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln
210 215 220

Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Thr Leu Trp Tyr Ser Asn Arg
225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly
245 250 255

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

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

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Ile Asn Trp Val
290 295 300

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

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Gln Val Lys Asp Arg
325 330 335

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
340 345 350

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
355 360 365

Ala Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
370 375 380

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
385 390 395 400

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
405 410 415

Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser
420 425 430

Tyr Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe
435 440 445

Val Val Ala Ile Asn Trp Ala Ser Gly Ser Thr Tyr Tyr Ala Asp Ser
450 455 460

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
465 470 475 480

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
485 490 495

Cys Ala Ala Gly Tyr Gln Ile Asn Ser Gly Asn Tyr Asn Phe Lys Asp
500 505 510

Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
515 520 525

His His His His His His
530

<210> 73
<211> 398
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 73
Val Val Gly Gly Gly Gly Thr Gln Thr Val Val Thr Gln Glu Pro Ser
1 5 10 15

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Ala Ser Ser
20 25 30

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
35 40 45

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Val
50 55 60

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
65 70 75 80

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
85 90 95

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

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

Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln

130

135

140

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 145 150 155 160

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

Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr
 180 185 190

Tyr Ala Asp Gln Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser
 195 200 205

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

Ala Val Tyr Tyr Cys Val Arg His Ala Asn Phe Gly Asn Ser Tyr Ile
 225 230 235 240

Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 245 250 255

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

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Thr Leu Ser Cys Ala
 275 280 285

Ala Ser Gly Arg Thr Phe Ser Ser Tyr Ala Met Gly Trp Phe Arg Gln
 290 295 300

Ala Pro Gly Lys Glu Arg Glu Phe Val Val Ala Ile Asn Trp Ala Ser
 305 310 315 320

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
325 330 335

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
340 345 350

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Gly Tyr Gln Ile Asn
355 360 365

Ser Gly Asn Tyr Asn Phe Lys Asp Tyr Glu Tyr Asp Tyr Trp Gly Gln
370 375 380

Gly Thr Leu Val Thr Val Ser Ser His His His His His His
385 390 395

<210> 74

<211> 518

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 74

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

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

Gly Met Ser Trp Val Arg Gln Gly Gly Gly Gly Gly Leu Asp Gly Asn
35 40 45

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

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

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

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser
100 105 110

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

Lys Pro Leu Gly Leu Gln Ala Arg Val Val Gly Gly Gly Gly Thr Gln
130 135 140

Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr
145 150 155 160

Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly Asn
165 170 175

Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu
180 185 190

Ile Gly Gly Thr Lys Phe Leu Val Pro Gly Thr Pro Ala Arg Phe Ser
195 200 205

Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln
210 215 220

Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Thr Leu Trp Tyr Ser Asn Arg

225		230		235		240									
Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gly	Gly	Gly
			245						250					255	
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Val	Gln	Leu	Val
		260						265					270		
Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	Ser	Leu	Lys	Leu	Ser
		275					280					285			
Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	Ala	Ile	Asn	Trp	Val
	290					295					300				
Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Arg	Ile	Arg	Ser
305					310					315					320
Lys	Tyr	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	Gln	Val	Lys	Asp	Arg
				325					330					335	
Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	Ala	Tyr	Leu	Gln	Met
			340					345					350		
Asn	Asn	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Val	Arg	His
		355					360					365			
Ala	Asn	Phe	Gly	Asn	Ser	Tyr	Ile	Ser	Tyr	Trp	Ala	Tyr	Trp	Gly	Gln
	370					375					380				
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
385					390					395					400
Ser	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly
				405					410					415	

Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Arg Phe Met Ile Ser Glu
420 425 430

Tyr His Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
435 440 445

Val Ser Thr Ile Asn Pro Ala Gly Thr Thr Asp Tyr Ala Glu Ser Val
450 455 460

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
465 470 475 480

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
485 490 495

Asp Ser Tyr Gly Tyr Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
500 505 510

His His His His His His
515

<210> 75

<211> 518

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 75

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

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

Gly Met Ser Trp Val Arg Gln Gly Gly Gly Gly Gly Leu Asp Gly Asn
35 40 45

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

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

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

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser
100 105 110

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

Ser Gly Gly Gly Gly Ser Gly Gly Val Val Gly Gly Gly Gly Thr Gln
130 135 140

Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr
145 150 155 160

Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly Asn
165 170 175

Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu
180 185 190

Ile Gly Gly Thr Lys Phe Leu Val Pro Gly Thr Pro Ala Arg Phe Ser

195

200

205

Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln
 210 215 220

Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Thr Leu Trp Tyr Ser Asn Arg
 225 230 235 240

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly
 245 250 255

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

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

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Ile Asn Trp Val
 290 295 300

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

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Gln Val Lys Asp Arg
 325 330 335

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
 340 345 350

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
 355 360 365

Ala Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
 370 375 380

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
385 390 395 400

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
405 410 415

Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Arg Phe Met Ile Ser Glu
420 425 430

Tyr His Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
435 440 445

Val Ser Thr Ile Asn Pro Ala Gly Thr Thr Asp Tyr Ala Glu Ser Val
450 455 460

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
465 470 475 480

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
485 490 495

Asp Ser Tyr Gly Tyr Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
500 505 510

His His His His His His
515

<210> 76

<211> 382

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 76

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

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Ala Ser Ser
20 25 30

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
35 40 45

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Val
50 55 60

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
65 70 75 80

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
85 90 95

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

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

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

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
145 150 155 160

Asn Lys Tyr Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu

165

170

175

Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr
 180 185 190

Tyr Ala Asp Gln Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser
 195 200 205

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

Ala Val Tyr Tyr Cys Val Arg His Ala Asn Phe Gly Asn Ser Tyr Ile
 225 230 235 240

Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 245 250 255

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

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Thr Leu Ser Cys Ala
 275 280 285

Ala Ser Arg Phe Met Ile Ser Glu Tyr His Met His Trp Val Arg Gln
 290 295 300

Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Thr Ile Asn Pro Ala Gly
 305 310 315 320

Thr Thr Asp Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
 325 330 335

Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Pro
 340 345 350

Glu Asp Thr Ala Val Tyr Tyr Cys Asp Ser Tyr Gly Tyr Arg Gly Gln
355 360 365

Gly Thr Gln Val Thr Val Ser Ser His His His His His His
370 375 380

<210> 77

<211> 503

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 77

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

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

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

Ala Gly Met Ser Ser Ala Gly Asp Arg Ser Ser Tyr Glu Asp Ser Val
50 55 60

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

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

Asn	Val	Asn	Val	Gly	Phe	Glu	Tyr	Trp	Gly	Gln	Gly	Thr	Gln	Val	Thr			
			100					105					110					
Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Glu	Val	Gln	Leu			
		115					120					125						
Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Asn	Ser	Leu	Arg	Leu			
	130					135					140							
Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Lys	Phe	Gly	Met	Ser	Trp			
145					150					155					160			
Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ser	Ser	Ile	Ser			
				165					170					175				
Gly	Ser	Gly	Arg	Asp	Thr	Leu	Tyr	Ala	Asp	Ser	Val	Lys	Gly	Arg	Phe			
			180					185					190					
Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Thr	Thr	Leu	Tyr	Leu	Gln	Met	Asn			
		195					200					205						
Ser	Leu	Arg	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Thr	Ile	Gly	Gly			
	210					215					220							
Ser	Leu	Ser	Val	Ser	Ser	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly			
225					230					235					240			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly			
				245					250					255				
Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala			
			260					265					270					
Ser	Gly	Phe	Thr	Phe	Asn	Lys	Tyr	Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala			

275

280

285

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

Asn Tyr Ala Thr Tyr Tyr Ala Asp Gln Val Lys Asp Arg Phe Thr Ile
 305 310 315 320

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
 325 330 335

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Ala Asn Phe
 340 345 350

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
 355 360 365

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 370 375 380

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
 385 390 395 400

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala
 405 410 415

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
 420 425 430

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Val Pro Gly Thr
 435 440 445

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
 450 455 460

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Thr Leu
465 470 475 480

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
485 490 495

Leu His His His His His His
500

<210> 78

<211> 509

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 78

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

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

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

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

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

Leu	Gln	Met	Asn	Ser	Leu	Arg	Pro	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Thr	Ile	Gly	Gly	Ser	Leu	Ser	Val	Ser	Ser	Gln	Gly	Thr	Leu	Val	Thr
			100					105					110		
Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Val
		115					120					125			
Val	Gly	Gly	Gly	Gly	Thr	Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu
	130					135					140				
Thr	Val	Ser	Pro	Gly	Gly	Thr	Val	Thr	Leu	Thr	Cys	Ala	Ser	Ser	Thr
145					150					155					160
Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn	Trp	Val	Gln	Gln	Lys	Pro
				165					170					175	
Gly	Gln	Ala	Pro	Arg	Gly	Leu	Ile	Gly	Gly	Thr	Lys	Phe	Leu	Val	Pro
			180					185					190		
Gly	Thr	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala
		195					200					205			
Leu	Thr	Leu	Ser	Gly	Val	Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys
	210					215					220				
Thr	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu
225					230					235					240
Thr	Val	Leu	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
				245				250						255	
Gly	Ser	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro

260

265

270

Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn
 275 280 285

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

Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
 305 310 315 320

Ala Asp Gln Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
 325 330 335

Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala
 340 345 350

Val Tyr Tyr Cys Val Arg His Ala Asn Phe Gly Asn Ser Tyr Ile Ser
 355 360 365

Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
 370 375 380

Gly Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
 385 390 395 400

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

Ser Arg Phe Met Ile Ser Glu Tyr His Met His Trp Val Arg Gln Ala
 420 425 430

Pro Gly Lys Gly Leu Glu Trp Val Ser Thr Ile Asn Pro Ala Gly Thr
 435 440 445

Thr Asp Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
450 455 460

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu
465 470 475 480

Asp Thr Ala Val Tyr Tyr Cys Asp Ser Tyr Gly Tyr Arg Gly Gln Gly
485 490 495

Thr Gln Val Thr Val Ser Ser His His His His His His
500 505

<210> 79

<211> 269

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 79

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Gln Ser Val Leu Thr Gln Pro Pro Ser Val
20 25 30

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Arg
35 40 45

Ser Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly
50 55 60

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

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
85 90 95

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
100 105 110

Ser Tyr Asp Arg Tyr Thr His Pro Ala Leu Leu Phe Gly Thr Gly Thr
115 120 125

Lys Val Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

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

Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
165 170 175

Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
180 185 190

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

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
210 215 220

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225 230 235 240

Val Tyr Tyr Cys Lys Thr His Gly Ser His Asp Asn Trp Gly Gln Gly

Thr Met Val Thr Val Ser Ser His His His His His His
260 265

<210> 80

<211> 5

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
Sortase A cleavage site"

<220>

<221> MOD_RES

<222> (3)..(3)

<223> Any amino acid

<400> 80

Leu Pro Xaa Thr Gly
1 5

<210> 81

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>

<221> SITE

<222> (1)..(25)

<223> /note="This sequence may encompass 1-5 'Gly Gly Gly Gly Ser'
repeating units"

<400> 81

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 82

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>

<221> SITE

<222> (1)..(20)

<223> /note="This sequence may encompass 1-5 'Gly Gly Gly Ser'
repeating units"

<400> 82

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

Gly Gly Gly Ser
20

<210> 83

<211> 7

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
protease-cleavable sequence"

<400> 83

Gly Pro Leu Gly Val Arg Gly

1 5

<210> 84

<211> 8

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
protease-cleavable sequence"

<400> 84

Ile Pro Val Ser Leu Arg Ser Gly

1 5

<210> 85

<211> 8

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
protease-cleavable sequence"

<400> 85

Val Pro Leu Ser Leu Tyr Ser Gly

1 5

<210> 86

<211> 10

<212> PRT

<213> Unknown

<220>

<221> source

<223> /note="Description of Unknown:
protease-cleavable sequence"

<400> 86
Ser Gly Glu Ser Pro Ala Tyr Tyr Thr Ala
1 5 10

<210> 87
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 87
Gly Gly Gly Gly Ser
1 5

<210> 88
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 88
Gly Ser Gly Ser Gly Ser
1 5

<210> 89
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 89

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Thr
1 5 10

<210> 90

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 90

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

<210> 91

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic 6xHis tag"

<400> 91

His His His His His His
1 5

<210> 92

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 92

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

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

Gly Met Ser Trp Val Arg Gln Gly Gly Gly Gly Gly Leu Asp Gly Asn
35 40 45

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

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

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

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile Gly Gly Ser Leu Ser
100 105 110

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